According to conventional wisdom, invasive fungal infections affect limited populations. These diseases tend to be cast as medical zebras even among people at greatest risk, including immunosuppressed patients and those residing in specific geographic areas of the United States. However, fungal disease epidemiology is changing. New risk groups have been identified, zoonotic epidemics with human spillover have taken hold, antifungal resistance has emerged, and previously defined endemic zones are expanding. Here we describe 4 of the most clinically consequential examples of emerging fungal infections. This overview does not cover the multi-drug-resistant *Candida auris* because it has been covered extensively elsewhere. Infectious disease specialists have and will continue to act on the front lines as fungal diseases continue to appear in new and curious places.

1. **AZOLE-RESISTANT ASPERGILLUS FUMIGATUS**

   *Aspergillus fumigatus* is a mold common in the environment, and most people breathe in *Aspergillus* spores every day without getting sick. It is the most common cause of invasive mold infections in...
#1 PRESCRIBED FOR ADULTS WITH HIV-1 STARTING AND SWITCHING ARV REGIMENS

**INDICATION**
BIKTARVY is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral (ARV) treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for ≥3 months with no history of treatment failure and no known resistance to any component of BIKTARVY.

**IMPORTANT SAFETY INFORMATION**

**BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**
- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY.
  - If appropriate, anti-hepatitis B therapy may be warranted.

**Contraindications**
- **Coadministration:** Do not use BIKTARVY with dofenilide or rifampin.

**Warnings and precautions**
- **Drug interactions:** See Contraindications and Drug Interactions sections. Consider the potential for drug interactions prior to and during BIKTARVY therapy and monitor for adverse reactions.
- **Immune reconstitution syndrome,** including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of BIKTARVY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate BIKTARVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
  - **Renal monitoring:** Prior to or when initiating BIKTARVY and during therapy, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

**Treatment-Naïve Study Designs**
- The efficacy and safety of BIKTARVY for treatment-naïve adults were evaluated in Study 1489 and Study 1490. In **Study 1489,** a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥50 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=314) or ABC/DTG/3TC (n=315) once daily. In **Study 1490,** a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥30 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=320) or FTC/TAF+DTG (n=325) once daily. The primary endpoint for both trials was the proportion of adults with HIV-1 RNA <50 copies/mL at Week 48. Secondary endpoints included efficacy, safety, and tolerability at Week 96.
THE BEAUTY OF POSSIBILITIES

BIKTARVY® combines the FTC/TAF® backbone with bictegravir, a novel and unboosted INSTI—for a powerful STR with a high barrier to resistance1,6

No Treatment-Emergent Resistance Associated With BIKTARVY Through Week 961,4,5,7

In two large phase 3 clinical trials in treatment-naïve adults1,5,7

> Among 634 treatment-naïve adults in Studies 1489 and 1490, 7 treatment-failure subjects were tested and no amino acid substitutions emerged that were associated with BIKTARVY resistance

Powerful Efficacy in Treatment-Naïve Adults1,5,7

Results noninferior to comparators at Week 481-3

Virologic Response

Results noninferior to comparators at Week 964,5,7

Virologic Response

Most common adverse reactions (incidence ≥5%; all grades) in treatment-naïve clinical studies through week 96 were diarrhea (6%), nausea (6%), and headache (5%).4,5

IMPORTANT SAFETY INFORMATION (continued)

Warnings and precautions (continued)

> Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue BIKTARVY if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Please see additional Important Safety Information for BIKTARVY, including BOXED WARNING, and Brief Summary of full Prescribing Information for BIKTARVY on following pages.

*emtricitabine 200 mg/tenofovir alafenamide 25 mg.
†95% confidence interval.
IMPORTANT SAFETY INFORMATION (continued)

Adverse reactions

- **Most common adverse reactions** (incidence ≥5%; all grades) in clinical studies through week 96 were diarrhea (6%), nausea (6%), and headache (5%).

Drug interactions

- **Prescribing information**: Consult the full prescribing information for BIKTARVY for more information on Contraindications, Warnings, and potentially significant drug interactions, including clinical comments.

- **Enzymes/transporters**: Drugs that induce P-gp or induce both CYP3A and UGT1A1 can substantially decrease the concentration of components of BIKTARVY. Drugs that inhibit P-gp, BCRP, or inhibit both CYP3A and UGT1A1 may significantly increase the concentrations of components of BIKTARVY. BIKTARVY can increase the concentration of drugs that are substrates of OCT2 or MATE1.

- **Drugs affecting renal function**: Coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and tenofovir and the risk of adverse reactions.

Dosage and administration

- **Dosage**: 1 tablet taken once daily with or without food.

- **Renal impairment**: Not recommended in patients with CrCl <30 mL/min.

- **Hepatic impairment**: Not recommended in patients with severe hepatic impairment.

- **Prior to or when initiating**: Test patients for HBV infection.

- **Prior to or when initiating, and during treatment**: As clinically appropriate, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus.

Pregnancy and lactation

- **Pregnancy**: There is insufficient human data on the use of BIKTARVY during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established. Available data from the APR for FTC shows no difference in the rates of birth defects compared with a US reference population.

- **Lactation**: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

Please see Brief Summary of full Prescribing Information for BIKTARVY on following pages.

BIKTARVY® (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx only.

**WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B**

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions].

**INDICATIONS AND USAGE**

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

**DOSE AND ADMINISTRATION**

Also see Warnings and Precautions and Use in Specific Populations.

**Testing Prior to or When Initiating:** Test patients for HIV infection.

**Testing Prior to or When Initiating, and During Treatment:** As clinically appropriate, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

**Dosage:** One tablet taken once daily with or without food.

**Renal Impairment:** BIKTARVY is not recommended in patients with CrCl <30 mL/min.

**Hepatic Impairment:** BIKTARVY is not recommended in patients with severe hepatic impairment.

**CONTRAINDICATIONS**

Also see Drug Interactions.

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

**WARNINGS AND PRECAUTIONS**

Also see BOXED WARNING, Contraindications, Adverse Reactions, and Drug Interactions.

Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV: Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating ARV therapy. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: Coadministration of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions; this may lead to loss of efficacy and development of resistance to BIKTARVY or clinically significant adverse reactions from greater exposures of concomitant drugs. Consider the potential for drug interactions and review concomitant medications prior to and during therapy. Monitor for adverse reactions associated with concomitant drugs.

**Immune Reconstitution Syndrome (IRS):** IRS has been reported in patients treated with combination ARV therapy. During the initial phase of treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is variable, and can occur many months after initiation of treatment.

**New Onset or Worsening Renal Impairment:** Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs in animal studies and human trials. In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs >30 mL/min, and in virologically suppressed subjects switched to BIKTARVY with eGFRs >50 mL/min, renal serious adverse events were encountered in less than 1% of subjects treated with BIKTARVY through Week 48. BIKTARVY is not recommended in patients with CrCl <30 mL/min. Patients taking tenofovir prodrugs who have renal impairment and/or are taking nephrotoxic agents including NSAIADS are at increased risk of developing renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. **Renal Monitoring:** Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

**Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF. Treatment with BIKTARVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

**ADVERSE REACTIONS**

Also see BOXED WARNING and Warnings and Precautions.

**In Adults with No ARV Treatment History:**

The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naïve adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

**Adverse Reactions:** Adverse reactions (all Grades) reported in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 and 1490, respectively were: diarrhea (6%, 3%), nausea (5%, 3%), headache (5%, 4%), fatigue (3%, 2%), abnormal dreams (3%, <1%), dizziness (2%, 2%), and insomnia (2%, 2%). Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicide occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

**Laboratory Abnormalities:** Laboratory abnormalities (Grades 3–4) occurring in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 or 1490, respectively were: amylase ≥2.0 x ULN (2%, 2%), ALT ≥5.0 x ULN (1%, 2%), AST ≥5.0 x ULN (2%, 1%), Creatinine Kinase ≥10.0 x ULN (4%, 4%), Neutrophil count >750 mm3 (2%, 2%), and fasting LDL-cholesterol >190 mg/dL (2%, 3%).

**Changes in Serum Creatinine:** Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Trials 1489 and 1490, median serum creatinine increased by 0.10 mg/dL from baseline to Week 48 in the BIKTARVY group and was similar to the comparator groups.

Continued on next page.
Continued from previous page.

**Changes in Bilirubin:** In Trials 1489 and 1490, total bilirubin increases were observed in 12% of subjects administered BIKTARVY through Week 48.

**In Virologically Suppressed Adults:** The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial in which virologically suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY.

**Adverse Reactions:** Overall, the safety profile in virologically suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

**DRUG INTERACTIONS**

Also see **Indications and Usage, Contraindications, and Warnings and Precautions.**

**Other Antiretroviral Medications:** BIKTARVY is a complete regimen for the treatment of HIV-1 infection, BIKTARVY coadministration with other ARV medications for treatment of HIV-1 infection is not recommended. Complete information regarding potential drug interactions with other ARV medications is not provided.

**Potential for BIKTARVY to Affect Other Drugs:** BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations.

**Potential Effect of Other Drugs to Affect BIKTARVY:** BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inhibitor of CYP3A and also an inducer of UGT1A1 may substantially decrease the plasma concentrations of BIC which may lead to loss of efficacy and development of resistance. The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC. TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of efficacy and development of resistance.

**Drugs Affecting Renal Function:** Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs, which may increase the risk of adverse reactions.

**Established and Potentially Significant Drug Interactions:** The listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY. An alteration in regimen may be recommended.

- Antiarrhythmics: dofetilide. Coadministration is contraindicated due to potential for serious and/or life-threatening events.
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Coadministration with alternative anticonvulsants should be considered.
- Antimycobacterials: rifampin. Coadministration is contraindicated due to the effect on BIKTARVY. Rifabutin, rifapentine. Coadministration is not recommended.
- Herbal Products: St. John’s wort. Coadministration is not recommended.
- Medications/oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Antacids containing Al/Mg or Calcium: BIKTARVY can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of BIKTARVY simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. Supplements containing Calcium or Iron: BIKTARVY and supplements containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.
- Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

Consult the full Prescribing Information prior to and during treatment with BIKTARVY for important drug interactions; this list is not all inclusive.

**USE IN SPECIFIC POPULATIONS**

Also see **Dosage and Administration, Warnings and Precautions, and Adverse Reactions.**

**Pregnancy:** Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. Risk Summary: There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. BIC and TAF use in women during pregnancy has not been evaluated; however, FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR.

**Lactation:** The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Based on published data, FTC has been detected in human milk; it is not known whether BIKTARVY or any of the components of BIKTARVY are present in human milk. The effects of BIKTARVY on the human breast milk have not been evaluated. FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR.

**Pediatric Use:** Safety and effectiveness of BIKTARVY in pediatric patients less than 18 years of age have not been established.

**Geriatric Use:** Clinical studies of BIKTARVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

**Renal Impairment:** BIKTARVY is not recommended in patients with severe renal impairment (CrCl <30mL/min). No dosage adjustment of BIKTARVY is recommended in patients with CrCl >30mL/min.

**Hepatic Impairment:** No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as BIKTARVY has not been studied in these patients.

**OVERDOSE:**

If overdose occurs, monitor the patient for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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Questions related to editorial content and submissions should be sent to Managing Editor Alexandra Ward, MA: AWARD@CONTAGIONLIVE.COM.
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HIV Infection in 2019: A Cure Is Not the Real News

The announcement of the London patient, the second person cured of HIV infection through hematopoietic stem cell transplant, sent waves through the media and spurred a series of inaccurate headlines that put HIV back into focus for people who do not think about it often. I personally received a series of text messages along the lines of "Did you hear about the HIV cure?" and "I heard there's someone in Europe with a cure for AIDS." Because these came from intelligent, nonmedical people, it led me to reflect on the paucity of knowledge that most people have about the breakthroughs in HIV management and therapies.

One-pill regimens have been a reality for HIV regimens since the approval of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) more than 10 years ago. This revolution has continued with integrase strand transfer inhibitor (INSTI)–based regimens earlier this decade. Regimens containing 3 drugs can be replaced with 2-drug regimens, sparing patients from exposure to a third agent. In many ways, therapy for HIV infection has become easier to manage than that of diabetes. However, this is not well known outside infectious diseases clinicians, and even many HIV care practitioners are hesitant to transition patients whose infection is undetectable on an older 3-drug regimen to a novel regimen that decreases antiretroviral exposure.

Pre-exposure prophylaxis (PrEP) has transformed HIV management. Patients at high risk who are taking a single, well-tolerated antiretroviral are well protected from HIV infection, as is the public, by a reduction in transmission. It is a true public health revolution. However, the benefit has reached communities that are at risk at varying levels. Coastal gateway cities that formerly had the highest incidence of HIV infection but have instituted PrEP programs have been replaced by cities in the Southeast. Cities with a high prevalence and that provide PrEP programs are seeing the incidence drop. Despite high coverage by insurance companies, only a small proportion of patients who could benefit from PrEP currently receive it. Much needs to be done to spread the word to primary care providers and other clinicians, including pharmacists, nurse practitioners, and physician's assistants, to screen and recommend PrEP when appropriate.

Finally, the U=U (undetectable=untransmittable) campaign has given a catchy title to an important principle but one that is not well known enough. It will take time to break down the stigma of HIV infection that has built up over decades, but overcoming that barrier is vitally important for the physical and mental health of millions of people. Using treatment as prevention may not be as catchy as "finding a cure" for HIV, but it is certainly much more realistic. Implementing this treatment will become easier as new long-acting maintenance injectable antiretrovirals become available in the near future.

These areas of HIV medicine have in common a lack of sufficient awareness. Each is a major step forward from early therapies, advancing HIV from a death sentence to a chronic condition to the next step, which is making it an uncommon chronic condition in the United States and carrying advances forward into other countries. We may not have a cure, but we have sure come a long way. Let’s make certain that everyone knows it.
PrEP Retention in Care—It Takes a Village

BY ANIRUDDHA (ANU) HAZRA, MD

As the adoption of pre-exposure prophylaxis (PrEP) for HIV prevention expands across the nation, retention in care (RIC) is a critical step in ensuring the efficacy of PrEP. Multiple sites have attempted to identify specific barriers and obstacles that disrupt the continuum of PrEP care for patients and providers.

A study examining PrEP programs at community health centers in Rhode Island, Mississippi, and Missouri found that among 171 patients prescribed PrEP, 72% were retained in care at 3 months, but that percentage declined to 57% at 6 months. Suboptimal RIC was attributed to a combination of structural and individual factors. Results from another study from a San Francisco, California, community health clinic echoed these findings, with structural barriers regarding insurance coverage and PrEP cost remaining challenges even in the presence of benefit navigators. Finally, a recent study from a Federally Qualified Health Center in Chicago, Illinois, focused on the care of gender and sexual minorities also found significantly suboptimal PrEP RIC. Just over 40% of patients were retained at 12 months, with only 15% of patients completing all quarterly visits. This study found insurance status and comorbid conditions to be drivers of RIC. All these studies concluded that further research is needed to better identify factors that can enhance or impede PrEP RIC.

In a recent Letter to the Editor, an interdisciplinary PrEP care model involving clinical pharmacists was discussed. Clinical pharmacist support in medication adherence models has been well established and found to be significantly effective in the management of chronic medical conditions such as hypertension, hyperlipidemia, and type 2 diabetes mellitus. However, the effect of pharmacy support in PrEP RIC has not yet been closely studied. In this unique PrEP care model from a Florida Veteran Affairs Health System, pharmacists assisted in screening and managing PrEP adherence, drug–drug interactions, adverse drug reactions, laboratory results, and at-risk behaviors. The PrEP pharmacist visits were conducted either face-to-face or over the phone, depending on patient preference. Between June 2013 and February 2018, 79 patients were initiated on PrEP, with 54% retained in care at the end of the study. The pharmacists also found that nearly 80% of patients had completed all quarterly visits during their first 12 months of therapy. More than 80% of pharmacist encounters were conducted over the phone. Although it comprised a modest sample size, this model does suggest clinical pharmacists may enhance PrEP RIC.

The expansion of PrEP across the country is instrumental in our efforts to achieve HIV elimination. The US Preventive Services Task Force has drafted a grade A recommendation for “the use of PrEP to reduce the risk of acquisition of HIV infection in persons at high risk of HIV infection.” We expect this recommendation to greatly benefit PrEP implementation in the United States; however, unless we are able to overcome the barriers to RIC, any success will be limited. Clinical pharmacists are a known excellent resource in promoting engagement in care and medication adherence. Although their role in PrEP implementation has not yet been well defined, incorporating them into an interdisciplinary PrEP care model may yield substantial results. References available at ContagionLive.com.
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treptococcal toxic shock syndrome (STSS) is a 
life-threatening disease caused by β-hemolytic strep-
tococci, with group A Streptococcus being the most 
common pathogen. Mortality rates vary but 
are estimated to be between 30% and 60%.1,2

For STSS skin infections, the Infectious Diseases 
Society of America (IDSA) recommends combi-
nation therapy of penicillin and clindamycin3 
along with surgical intervention.

Clindamycin is recommended because of its ability 
to suppress streptococcal toxin and cytokine produc-
tion. Additionally, clindamycin has demonstrated efficacy 
in animal models and observational studies.4 Penicillin 
is also recommended because of potential resistance of 
group A Streptococcus to clindamycin. Although macrolide 
resistance is low in the United States, other countries have 
seen increased resistance rates to macrolides. Macrolides 
and clindamycin are not chemically related, but they share 
a similar mechanism of action, and many of these macro-
lide-resistant strains are also resistant to clindamycin.

Intravenous immunoglobulin (IVIG) has been suggested 
as adjunctive therapy to neutralize antibodies produced in 
response to streptococcal virulence factors and to inhibit 
the production of proinflammatory cytokines.5 However, 
controversy exists regarding the use of IVIG as adjunctive 
therapy, as IDSA guidelines do not recommend its routine 
use because of conflicting mortality benefit results and 
controversy exists regarding the use of IVIG in STSS. Further, 
the lone prospective study of IVIG in STSS was terminated 
early because of slow enrollment.

A recent review and meta-analysis evaluated the mortality 
rate in studies evaluating adjunctive IVIG for patients 
treated with clindamycin for STSS.6 Previous studies had 
been complicated by the inherent risk of bias, the variable 
 inclusion criteria, and the inconsistent use of clindamycin. 
Therefore, to combat bias, the authors used a Cochrane 
collaboration risk assessment tool.7 A meta-analysis was 
performed using a random-effects model and assessed 
heterogeneity using the $I^2$ statistic, with the primary 
measure being the risk ratio (RR) for death at 30 days.

Five studies (1 randomized and 4 nonrandomized) met 
inclusion criteria from 1992 to 2009. One study was in chil-
dren only, 1 study included children and adults, and the 
other 3 studies were in adults only. The primary outcome 
in each study was mortality at either 28 or 30 days. One 
hundred and sixty-five patients with STSS treated with 
clindamycin were included; among these, 70 patients also 
received IVIG. The overall mortality rate was 26.1%, ranging 
from 14.3% to 40.5% in individual studies. In the individual 
 studies, IVIG administration was associated with lower 
mortality rates but was not statistically significant. However, 
in the pooled analysis, adjunctive IVIG administration in 
combination with clindamycin therapy was associated with 
a reduction in mortality from 33.7% to 15.7% (RR, 0.46; 95% 
CI, 0.26-0.83; $P = .01$), with negligible heterogeneity ($I^2 = 0$).

Although this was a meta-analysis, a limitation of the 
study still includes the small sample size, which may lack 
effect precision. Another limitation is that differences in baseline 
characteristics between groups may lead to confounding, with the 
authors acknowledging that the reduction in mortality rates asso-
ciated with IVIG use could be due to confounding. A third limitation 
is that there was limited information on concomitant antibiotics, 
optimal dosing of IVIG, and length of therapy.

Without a large randomized, controlled trial, this study provides 
valuable insight and suggests advantageous effects of adjunctive IVIG in the treatment of 
STSS with clindamycin. Additionally, given that the condi-
tion is relatively rare and the previous valiant effort to 
 enroll in a randomized, controlled trial proved futile, an 
international STSS registry, similar to the data collected 
by the ARDS Network, may help to provide more data and 
strengthen the recommendations (Table).

References available at ContagionLive.com.

| TABLE. Mortality Rate of Adjunctive IVIG for Patients Treated With Clindamycin for STSS |
|---|---|---|---|
| STUDY | TYPE | YEAR | RR (95% CI) | DEATHS/CASE PATIENTS (MORTALITY RATE) | DEATHS/CONTROL PATIENTS (MORTALITY RATE) |
| Kaul et al13 | Nonrandomized | 1999 | 0.57 (0.25-1.27) | 6/20 (30.0%) | 9/17 (52.9%) |
| Adalat et al14 | Nonrandomized | 2014 | 0.22 (0.01-3.81) | 0/8 (0%) | 3/13 (23.0%) |
| Carapetis et al15 | Nonrandomized | 2014 | 0.31 (0.04-2.29) | 1/13 (7.7%) | 6/24 (25.0%) |
| Linner et al16 | Nonrandomized | 2014 | 0.40 (0.13-1.27) | 3/21 (14.3%) | 11/31 (35.5%) |
| Subtotal of nonrandomized | Nonrandomized | 2018 | 0.47 (0.25-0.86) | 10/62 (16.1%) | 29/85 (34.1%) |
| Darenberg et al17 | Randomized | 2003 | 0.42 (0.05-3.28) | 1/8 (12.5%) | 3/10 (30.0%) |
| Pooled | N/A | 2018 | 0.46 (0.26-0.83) | 11/70 (15.7%) | 32/95 (33.7%) |

IVIG indicates intravenous immunoglobulin; N/A, not applicable; RR, risk ratio; STSS, streptococcal toxic shock syndrome.
Typhus Outbreak Strikes Los Angeles, but the City Is Not Alone: Public Health Watch
By Brian P. Dunleavy

Los Angeles County Department of Public Health is investigating an outbreak of flea-borne typhus cases in downtown Los Angeles.

Typhus is endemic to the county and on average about 60 cases are reported each year. This situation is unique because of the high number of cases reported in a short amount of time.

According to a report in the Los Angeles Times, there were 19 cases of the age-old disease among the city’s homeless population, centered in the downtown area, in late 2018. This outbreak may be part of a growing trend. According to state health data cited by the Times, there were 167 cases of typhus in California in 2018 compared with just 13 in 2008.

In all, 95% of those infected last year resided in Los Angeles and Orange counties.

"Rodents are the [primary] reservoir for typhus, but opossums and domestic pets can also play a role with bringing infected fleas into the living environment," said Kristy Murray, DVM, PhD, professor of pediatric tropical medicine and molecular virology at Baylor College of Medicine and director of the Center for Human Immunobiology at Texas Children's Hospital, in explaining the challenges facing Los Angeles and other large cities across the United States. Murray and her team have published several reports on typhus outbreaks, including one in the December 2017 issue of Emerging Infectious Diseases, which described 18 confirmed cases among children in Houston.

Investigators Develop Tool to Measure Intact HIV Proviruses
By Jonna Lorenz

A new tool may accurately assess the HIV reservoir in patients and could help target treatment of the disease, according to a research letter published in the journal Nature.

The assay can accurately distinguish between intact and defective proviruses that lie latent within infected cells and will enable physicians to determine the extent to which their interventions are effective.

"It’s a technical advance to allow us to accurately assess the size and the extent of the reservoir," Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), told Contagion®, calling the reservoir "one of the real stumbling blocks in curing HIV infection."

Funded by NIAID, which is part of the National Institutes of Health, the research examined 431 HIV-1 genome sequences taken from 28 patients with HIV-1 undergoing suppressive antiretroviral therapy. The team mapped deletions and lethal mutations and then developed genetic probes to distinguish flawed proviruses from intact proviruses. Using a nanotechnology method, the team counted the number of intact proviruses.

Among the 28 patients, 24 had suppression of viruses in the blood for longer than 6 months when studied and 5 showed viruses in the blood. Defects in the proviruses varied depending on when the antiretroviral therapy was started and the amount of virus detectable in the blood.

The study found that 2.4% of proviruses were intact, leaving 97.6% with fatal defects. Notably, the intact proviral DNA assay was able to identify and exclude those proviruses with defects. This will help inform providers targeting the intact proviruses that stand in the way of curing the infection.

VOICE Trial: Daily Vaginal Tenofovir Gel Use Reduces Genital Herpes Risk in Women
By Einav Keet

Genital herpes simplex virus type 2 (HSV-2) infection increases the risk of acquiring and transmitting HIV, particularly in areas of sub-Saharan Africa where HIV is highly prevalent. Results from a new study suggest that women who consistently used a vaginal tenofovir (TFV) gel for pre-exposure prophylaxis (PrEP) saw a reduced risk of HSV-2 and HIV-1 acquisition.

The new manuscript, published in the Journal of Infectious Diseases, provides information on the VOICE study, a large, randomized, placebo-controlled trial of HIV-1 PrEP products, including oral tenofovir disoproxil fumarate and vaginal TFV 1% gel.

The trial enrollment was conducted across 15 sites in South Africa, Uganda, and Zimbabwe. Enrolled participants were women aged 18 to 45 years who were neither pregnant nor breast-feeding and had normal renal, hematologic, and hepatic function.

"No biomedical prevention method currently exists for HSV-2, the most common cause of genital herpes," explained study coauthor Jeanne Marrazzo, MD, MPH, FACP, FIDSA, director of the Division of Infectious Diseases and professor of medicine at the University of Alabama, Birmingham, in an interview with Contagion®.

A total of 1004 enrolled participants were randomized to receive TFV gel, of whom 438 (44%) were HSV-2 seropositive and 566 (56%) were seronegative. Among women who were seronegative at enrollment, 92 acquired HSV-2 over a median time of 1 year, and investigators found that adherence to study products was low overall, especially among younger, unmarried women, who had the highest incidence of HIV-1 and HSV-2.

In a secondary analysis, though, investigators used plasma measurement of TFV to measure product use and detection of TFV in the plasma of 130 (24%) participants. The investigators found that overall regular use of TFV gel was associated with a 40% reduction in HSV-2 acquisition.
FDA Grants Breakthrough Therapy Designation for Investigational Drug for Recurrent C Difficile Infection

By Michaela Fleming

The US Food and Drug Administration has granted a breakthrough therapy designation to investigational drug CP101 for the treatment of recurrent Clostridium difficile infection, Finch Therapeutics has announced.

The drug is being developed to address an unmet need in C difficile prevention. Recurrent C difficile has been designated an urgent public health threat by the US Centers for Disease Control and Prevention because of the high percentage of patients failing standard-of-care treatment.

Finch Therapeutics reports that participants are currently being enrolled in the randomized, placebo-controlled phase 2 PRISM3 trial. The study will assess the safety and efficacy of the drug, which will be administered in a single dose through an oral capsule.

Participants who enroll in the study will be assigned at random to receive the investigational drug or a placebo. Over a 6-month period, the participants will meet with clinical staff 7 times to have their health and progress evaluated. Participants will also submit stool samples throughout the study using at-home collection kits.

Fighting Flu With Math: Predicting Peak Season, Spread, and Vaccination Patterns

By Alexandra Ward, MA

A team of investigators at New York University (NYU) has developed a unique strategy to fight influenza.

Flu activity in the United States continues to rise, with the percentage of people visiting their health care providers for flu-like illnesses up in the week ending February 5, 2019, according to the US Centers for Disease Control and Prevention’s weekly FluView.

Using a mathematical model, developed by NYU professor Maurizio Porfiri, PhD, MSc, and 2 Italian investigators with visiting appointments at NYU, analyzes epidemiological and sociological factors to predict when the influenza season will peak, whom should be vaccinated, when vaccinations should occur, and whether to quarantine infected patients, according to a study published by the Society for Industrial and Applied Mathematics in the SIAM Journal on Applied Dynamical Systems.

“Human behaviors are characterized by nonhomogeneous temporal distributions. For instance, periods of high social activity typically alternate with periods characterized by a moderate social life. This phenomenon is called burstiness,” Lorenzo Zino, PhD, an investigator at Politecnico di Torino in Italy who worked on the study, told Contagion®.

The investigators combined this burstiness metric along with the more traditional details about the infectious disease itself and the spatial and temporal properties of the network of social interactions and “activity-driven networks.” The result was a computer simulation that is able to act as humans do to predict flu trajectory.

HPV Vaccination Rates Fall Short in Adolescents

By Jonna Lorenz

US adolescents have fallen behind recommended schedules for human papillomavirus (HPV) vaccinations, according to a study published in the Journal of Infectious Diseases.

Although approximately 60% of 13- to 17-year-old adolescents had initiated the vaccine series in 2016, only 16% of adolescents had completed the series by age 13, and 35% had completed the vaccination by age 15, according to the study, which examined 2016 data from an annual US Centers for Disease Control and Prevention survey of parents on teen immunizations.

“What we really see is that adolescents are getting the vaccine; they’re just tending to get it at slightly older ages,” Robert A. Bednarczyk, PhD, assistant professor in the Hubert Department of Global Health and the Department of Epidemiology at the Emory University Rollins School of Public Health and lead author of the study, told Contagion®.

The Advisory Committee on Immunization Practices recommends HPV vaccination before age 13. Only 2 doses of the vaccine are needed if completed before age 15.

An additional benefit of administering the vaccine at younger ages is that it may induce a stronger immune response.
Integrase strand transfer inhibitors (INSTIs), when combined with 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs), make up the bulk of first-line HIV therapy regimens. With over 30 drugs approved for the treatment of HIV infection, the regimen choice is often determined by concerns over pill burden, tolerability and/or toxicity, and barrier to resistance.

Biktarvy is a fixed-dose, single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide. It received FDA approval on February 7, 2018, for treatment-naïve patients with HIV or those already virologically suppressed on an antiretroviral therapy regimen for at least 3 months with no known resistance to any of the drug components. Two of the 3 drug components, emtricitabine and tenofovir alafenamide, are already part of other first-line therapy regimens and are known to be safe and well tolerated by most patients. Biktarvy is a new, highly active INSTI with both a high barrier to resistance and few drug–drug interactions. These advantages have allowed Biktarvy to quickly become a regimen of choice among HIV health care providers.

**CLINICAL STUDIES**

Biktarvy was studied in 4 phase 3 trials, 2 in treatment-naïve patients who were HIV-1 positive and 2 in virologically suppressed patients. Study 1489 was a noninferiority trial that randomized 629 treatment-naïve adults 1:1 to either Biktarvy or abacavir/dolutegravir/lamivudine (Triumeq) for 144 weeks. The primary end point was HIV viral load of less than 50 at week 48, and the noninferiority margin was set at 12%. The end point was achieved in 92.4% of patients receiving Biktarvy and 93.0% in those in the abacavir/dolutegravir/lamivudine group, with a difference of 0.6% (CI, –4.8 to 3.6). Neither group had any documented resistance to the study drugs. Interestingly, patients in the Biktarvy group had fewer adverse effects, mainly because of lower rates of nausea (5% vs 17%, respectively; \( P < .0001 \)) (Table).

Study 1490 compared Biktarvy to combination dolutegravir/emtricitabine/tenofovir alafenamide (Tivicay and Descovy). This study was again conducted in treatment-naïve adults who were HIV-1 positive, with the same primary end point of HIV viral load of less than 50 at the end of 48 weeks with a noninferiority margin of 12%. A total of 657 adults were randomized 1:1 to Biktarvy or dolutegravir/emtricitabine/tenofovir alafenamide. At week 48, 89% of patients in the Biktarvy group and 93% in the dolutegravir group met the predetermined end point (difference of 3.5%; CI –7.9 to 1.0), which met noninferiority criteria. No resistance emerged in either group.

**Biktarvy: A Regimen of Choice for HIV Therapy**

The new single-tablet regimen provides a safe and effective treatment option for patients with HIV.

By Brionna Matt, DO

Matt is a board-certified internal medicine physician in her second year of infectious disease fellowship at Temple University Hospital in Philadelphia, Pennsylvania. She completed her medical education at Philadelphia College of Osteopathic Medicine and her internal medicine residency at Lankenau Medical Center in Wynnewood, Pennsylvania.
The adverse effects were similar between the 2 groups, with headache and gastrointestinal upset being the most common.²

The other 2 studies evaluated switching adults who were HIV-1 positive and already stably virally suppressed on a different regimen to Biktarvy. Study 1878 evaluated 577 patients on a stable boosted protease inhibitor plus a dual-NRTI backbone regimen and then randomized half of them to switch to Biktarvy. The individuals had to be on their prior regimen for at least 6 months and have a viral load of less than 50 for at least 6 months. They could not have had previous exposure to other INSTIs. Biktarvy was being compared with a regimen of either boosted atazanavir or darunavir with a backbone of tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine. The patients were randomized 1:1 to either group, with the primary end point being the proportion of patients at week 48 with a viral load of 50 or higher. In each group, 5 subjects had a viral load of 50 or higher at week 48 (2%).³

Finally, study 1844 assessed switching from abacavir/dolutegravir/lamivudine in virologically suppressed patients to Biktarvy. The study randomized patients 1:1 to either agent and assessed an end point of virological failure using viral loads of 50 or higher at 48 weeks. This occurred in 3 of 248 patients (1%) in the Biktarvy group and 1 of 281 (<1%) in the abacavir/dolutegravir/lamivudine arm.⁴

ADVERSE REACTIONS AND PRECAUTIONS
Multiple considerations need to be addressed before prescribing Biktarvy. It is not recommended in patients with a creatinine clearance of less than 30 or in those with severe hepatic impairment. Although drug interactions are minimal, Biktarvy cannot be given concomitantly with rifampin or dofetilide. Furthermore, clinicians must follow guideline recommendations to test patients for hepatitis B prior to use because emtricitabine and tenofovir alafenamide are components. This remains as a black box warning for abrupt discontinuation of this medication in patients with hepatitis B, as it can lead to severe and acute exacerbations.⁵

PLACE IN THERAPY
Biktarvy represents another advance in the treatment of HIV infection. Studies support Biktarvy as a safe and effective new HIV therapy. As we continue to improve our options for HIV management, it is understandable that providers are increasingly turning to Biktarvy over the other first-line regimens. Biktarvy requires no additional lab testing (eg, for HLA-B27), a limit of other first-line agent abacavir/dolutegravir/lamivudine. The high barrier of resistance and once-daily formulation, along with no restrictions on taking it with or without food, make it particularly attractive for many of our patients. Additionally, Biktarvy remains a good alternative for virologically suppressed patients who are on more toxic regimens. ▲

References are available at ContagionLive.com.
EMERGING & RE-EMERGING INFECTIONS

Four Fungal Horsemen: Emerging Trends in Fungal Disease Epidemiology

New public health perspectives on aspergillosis, sporotrichosis, histoplasmosis, and coccidioidomycosis.

BY HILARY C. KELLY, MPH; MICHAEL B. HENRY, MD AND MS CANDIDATE; BRENDAN R. JACKSON, MD, MPH; AND KARLYN D. BEER, PHD, MS

Aspergillus fumigatus is a mold common in the environment, and most people breathe in Aspergillus spores every day without getting sick.

Aspergillus fumigatus is a mold common in the environment, and most people breathe in Aspergillus spores every day without getting sick.

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Kelly is an Oak Ridge Institute for Science and Education fellow in the Mycotic Diseases Branch at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, working on invasive mold infection surveillance.

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people who are immunocompromised and have lung diseases, and mortality from invasive aspergillosis is high (>25%). The development of azole antifungal medications such as voriconazole, itraconazole, and posaconazole has greatly improved survival since the late 1990s; however, infections caused by azole-resistant A. fumigatus have emerged. This resistance was first detected in Europe but has now been found across the globe, including recently in the United States. Azole resistance in A. fumigatus is associated with treatment failure and mortality rates greater than 88%. Of primary concern are azole-resistant A. fumigatus strains associated with the use of azole agricultural fungicides. Although not a plant pathogen, A. fumigatus can develop resistance during incidental exposure to azole fungicides applied to treat and prevent fungal disease in crops. When these resistant strains cause invasive infections in humans, the efficacy of azole antifungal drugs is reduced. Agricultural azole use has increased in recent decades; in the United States, usage has increased by more than 500% from 2000 (579 metric tons) to 2015 (2940 metric tons). Environmental fungicide–associated A. fumigatus has been found in patients without a history of taking azole medications, supporting the idea that these resistant strains originated in the environment and not during prolonged azole therapy.

The geographic extent of IPA in patients with severe influenza is unknown outside the Netherlands and Belgium; it submission can be found at cdc.gov/fungal/aspergillus-resistance.html. Clinicians should consider azole- resistant aspergillosis in patients who do not respond to antifungal treatment, even in patients who are azole naive, although other causes of treatment failure exist.

2. INVASIVE PULMONARY ASPERGILLOSIS AND SEVERE INFLUENZA

Invasive pulmonary aspergillosis (IPA) affects primarily patients immunocompromised by stem cell or organ transplantation, chemotherapy, or immunosuppressive medications. However, in the past decade, A. fumigatus has emerged as a complication among patients with severe influenza requiring intensive care unit (ICU) admission. Since 2010, several US cases of IPA following severe influenza have been reported. However, findings from a recent multicenter study in Belgium and the Netherlands suggest that this condition may be more common than anticipated in some regions. The study found that about 20% of 432 ICU patients with severe influenza developed IPA within 3 days of ICU admission. About half of those who developed IPA were not immunocompromised. Patients with IPA in severe influenza have developed a rapidly progressive tracheobronchitis, with mortality rates of 46% to 61%. Aspergillus fumigatus may invade lung tissue in the absence of a compromised immune system through disruption of the respiratory epithelium from severe influenza. The geographic extent of IPA in patients with severe influenza is unknown outside the Netherlands and Belgium; it
may be a novel phenomenon or previously present but unrecognized. Until more definitive research and surveillance can answer this question, it is important for clinicians to consider diagnosis and treatment of invasive aspergillosis in patients with severe influenza who are not getting better with treatment, even in those who are not immunocompromised. Fungal culture or galactomannan antigen testing of bronchoalveolar lavage fluid can aid in diagnosis.

3. ZOONOTIC SPOROTRICHOSIS

Sporothrix brasiliensis behaves quite differently from sporotrichosis caused by the better-known Sporothrix schenckii. Although the symptoms of S. brasiliensis infection in humans often resemble those of S. schenckii infection, classically a localized skin ulceration with spreading lymphangitis, S. brasiliensis infections appear more virulent, with up to 20% of cases progressing to disseminated disease. Additionally, these infections may fail to respond to antifungal therapy. However, the major difference between these Sporothrix species is in how these infections are acquired. Sporotrichosis from S. schenckii is also known as rose gardener’s disease because it is frequently caused by traumatic inoculation from plants, whereas cats are the main reservoir and source of transmission of S. brasiliensis, making this an emerging zoonotic disease.

In cats, S. brasiliensis causes primarily facial ulcerations (Figure 1), typically after the cat is scratched or bitten by an infected or colonized cat. Feline-to-human transmission similarly occurs through scratches, bites, or contact with lesions of infected cats. Before 1990, S. brasiliensis was found only in the southeast region of Brazil, around São Paulo and Rio de Janeiro. Since then, it has spread throughout much of southern Brazil, with thousands of cases in humans and cats reported at a single center in Rio de Janeiro since 1998.

Given the close contact cats often have with people, and the tens of millions of stray cats in the United States and elsewhere, there is concern that this outbreak could spread to other areas as it has within Brazil. Clinicians, particularly infectious disease physicians, dermatologists, and veterinarians, should be aware of this emerging disease, as early identification will be key in minimizing spread of this fungus.

4. US ENDEMIC MYCOSES: COCCIDIOIDOMYCOSIS AND HISTOPLASMOSIS

Many physicians have been trained to associate endemic fungal diseases with specific geographic areas. However, a growing body of evidence suggests that for the fungi that cause these diseases, classical endemic ranges have expanded.

In the United States, coccidioidomycosis (commonly called valley fever), caused by Coccidioides, occurs mainly in Arizona and Southern California (Figure 2). Histoplasmosis is normally thought to exist in areas around the Mississippi and Ohio river valleys. However, these observations are based on half-century-old studies. Outside these ranges, physicians may not consider these illnesses in the differential diagnosis for many patients. For example, both fungal infections may be clinically indistinguishable from bacterial community-acquired pneumonia, and both can cause lung nodules that mimic lung cancer, leading to unnecessary treatments and delays in appropriate therapy.

Locally acquired coccidioidomycosis cases have been recorded as far north as Washington State, and soil samples linked to these cases tested positive for Coccidioides. Similarly, histoplasmosis can cause infections far outside its classical range, as suggested by animal cases as far away as Alaska and human cases reported to public health departments north of the endemic areas identified in the 1950s, specifically in Michigan, Minnesota, and Wisconsin.

Some have hypothesized that climate change and human activities are contributing to expanding geographic ranges, although increased detection capacity or other factors may be involved. Increasing periods of drought and higher temperatures in the West interspersed with high rainfall are thought to be conducive to Coccidioides growth in the soil and airborne dispersal under the “grow and blow” hypothesis. Likewise, climate and land-use changes could be contributing to a widening of the regions with soils that are well suited for Histoplasma. Whatever the reason for the apparent spread of these endemic fungi, practitioners outside these regions should consider these infections as possible causes of illness.

CONCLUSIONS

Fungi grow in vastly diverse environments, which occasionally include the bodies of humans and animals. Although the ecological factors associated with fungal disease are complex and poorly understood, the 4 examples described here highlight the need for vigilance as new fungal diseases emerge and familiar ones morph in range and risk groups. As epidemiologists aim to quantify the burden and longitudinal trends in fungal disease, our surveillance systems need to keep pace with the changing fungal world. Among the 4 fungal diseases discussed, only 1 (coccidioidomycosis) is nationally notifiable. Improved public health surveillance for these diseases could serve clinical and public health practices alike, by informing patient care and public health policy.

References are available at ContagionLive.com.
Treating Outpatient Cystitis in the Era of Antimicrobial Resistance

What can clinicians do now that increasing resistance has limited oral treatment options for outpatient cystitis?

BY RICARDO A. CAMARGO, PHARMD CANDIDATE, AND STEPHANIE E. GIANCOLA, PHARMD, BCPS, BCIDP

(continued from cover page)

RISK FACTORS FOR RESISTANCE

Although UTIs can be caused by several different pathogens, *Escherichia coli* remains the most common; however, the prevalence of multidrug-resistant (MDR) isolates among outpatients is increasing. Cystitis classification ( uncomplicated vs complicated ) can be important in determining the risk for an MDR organism. Patients typically considered to have uncomplicated infection include nonpregnant premenopausal women without significant comorbidities or urologic abnormalities. These patients are generally at lower risk for MDR organisms. Structural and functional abnormalities of the genitourinary tract (such as urethral catheterization, ureteral stent, neurogenic bladder, and benign prostatic hypertrophy) are considered to be complicating factors of a UTI and generally put the patient at higher risk for MDR pathogens. Additional risk factors for MDR cystitis include prior antimicrobial use, recurrent UTIs, recent hospitalization, nursing home or long-term care facility residence, regular hemodialysis clinic visits, urologic procedures within the past 3 months, chronic conditions (such as diabetes mellitus), and older age.

ORAL ANTIBIOTIC TREATMENT OPTIONS

The selection of antimicrobial treatment for outpatient cystitis requires assessment of risk factors for resistance as well as allergy history, adverse effect profile, drug interaction potential, and previous urine culture data, if available.

Fluoroquinolones (FQs) and trimethoprim/sulfamethoxazole (TMP/SMX) are among the most commonly prescribed antibiotics for UTIs. These antibiotics continue to be highly effective for UTIs caused by susceptible pathogens; however, resistance rates to UTI pathogens have increased within the past 10 years. For example, approximately 30% and 26% of more than 200,000 urinary *E. coli* isolates collected from adult Veterans Affairs (VA) outpatients between 2009 and 2013 were resistant to FQs and TMP/SMX, respectively. MDR pathogens often carry concurrent resistance genes to these and other antibiotics. This is demonstrated by the high rates of resistance to FQs and TMP/SMX among MDR urinary Enterobacteriaceae in several studies, ranging from 57% to 98% for TMP/SMX and 48% to 98% for FQs. Therefore, these antibiotics are not
recommended for empiric treatment of UTIs in patients with risk factors for resistance. They remain excellent choices for definitive therapy, even in MDR strains when susceptibility is detected, though most UTIs are treated empirically.

Oral β-lactams (such as amoxicillin-clavulanate and cefpodoxime) generally have inferior efficacy compared with first-line agents for cystitis; however, they may be used as alternative agents when first-line agents are not available.² Years of use of this class of antibiotics has also produced increased resistance rates for E coli and other UTI pathogens. For example, resistance rates of urinary E coli isolates among adult VA outpatients were 37% for amoxicillin-clavulanate or ampicillin-sulbactam but only 5.4% for extended-spectrum cephalosporins.¹¹ Oral cephalosporins may be active against some MDR isolates with resistance profiles not involving extended-spectrum β-lactamases (ESBLs), such as resistance to ampicillin, early-generation cephalosporins, TMP/SMX, FQs, and/or aminoglycosides. It is important to note that the Clinical and Laboratory Standards Institute (CLSI) M100 document indicates that cefazolin susceptibilities should be used to predict susceptibility to oral cephalosporins, not intravenous third-generation cephalosporins.¹² If an isolate is resistant to cefazolin but susceptible to intravenous third-generation cephalosporins (such as ceftriaxone), it may be appropriate to test the oral cephalosporin agents individually if needed for treatment, as some agents may remain susceptible.

Nitrofurantoin was approved by the US Food and Drug Administration in 1953 for the treatment of lower urinary tract infections; because of its low serum and tissue levels, however, it should not be used for the treatment of pyelonephritis, prostatitis, or complicated disease. Many studies have demonstrated that nitrofurantoin is as effective as other antibiotic options, with cure rates of approximately 79% to 92%, and could be given for a duration as short as 5 days.²³ Additionaly, nitrofurantoin has retained high susceptibility rates despite several decades of use.¹³ It has even demonstrated retained activity against US outpatient MDR E coli isolates (75%-98% susceptible).² In a small retrospective study completed in Turkey, a 14-day course of nitrofurantoin demonstrated clinical and microbiological success rates of 69% and 68%, respectively, in 75 patients with cystitis due to ESBL-producing E coli.²⁴ Therefore, nitrofurantoin may represent a suitable oral option in patients with cystitis due to ESBL-producing E coli. Additional clinical data evaluating the efficacy of nitrofurantoin in the treatment of cystitis due to MDR organisms are limited. Of note, although nitrofurantoin was previously recommended only in patients with a creatinine clearance of >60 mL/min, the American Geriatrics Society Beers Criteria now support its use in patients with a creatinine clearance of ≥30 mL/min.²⁵

Similar to nitrofurantoin, fosfomycin is an older antibiotic that has also retained activity against urinary pathogens.²⁶ In addition, fosfomycin demonstrated high susceptibility rates (96%) among 95 ESBL- or AmpC-producing urinary E coli isolates at 3 Canadian hospitals from 2015 to 2016.²⁷ Although a single-dose regimen has been well studied for uncomplicated cystitis due to antibiotic-susceptible organisms, there is less guidance available for the treatment of complicated or MDR cystitis. The most commonly used regimen for these infections is the off-label 3-dose regimen (given every 48-72 hours).²⁸,²⁹ The clinical efficacy of fosfomycin for the treatment of MDR cystitis has been evaluated in several nonrandomized studies. For example, in a retrospective study of 41 patients with a UTI due to an MDR organism, 59% had microbiological cure (70% for those with ESBL-producing E coli or Klebsiella pneumoniae).³⁰ In another study, the clinical and microbiological success rates were 94% and 79%, respectively, among 52 patients with cystitis due to ESBL-producing organisms.³¹ These data suggest that fosfomycin may be an effective option for MDR UTIs. However, it should be noted that fosfomycin susceptibility rates are generally lower among Klebsiella and Pseudomonas isolates, and resistance may develop while patients are on fosfomycin for UTIs caused by Pseudomonas.³²,³³ A potential barrier to the routine use of fosfomycin in the clinical setting is the lack of routine susceptibility testing in most microbiology laboratories. Therefore, providers typically need to ask their microbiology lab for specific susceptibility testing for this antibiotic. Additionally, CLSI breakpoints are established only for E coli and Enterococcus faecalis³⁴; therefore, clinicians should use caution in extrapolating these breakpoints to other organisms.

**NEED FOR INTRAVENOUS THERAPY**

As resistance rates continue to increase among outpatient urinary pathogens, the number of patients who can be treated with oral treatment options is decreasing. In patients with risk factors for resistant organisms and recent use or previous failure of nitrofurantoin or fosfomycin, it may be reasonable to initiate therapy with parenteral antibiotics while awaiting culture and susceptibility results. Initial intravenous antibiotics may also be considered for patients with multiple risk factors for resistance or multiple antibiotic allergies or for whom there is concern about more severe or systemic infection or infection with Pseudomonas.

**CONCLUSIONS**

Increasing antimicrobial resistance has limited oral antibiotic selection for outpatient cystitis treatment. Therefore, risk factors for resistance, antibiotic history, previous culture data, antibiotic allergy history, concomitant medications, and severity of infection should be carefully considered when choosing an antibiotic regimen for patients presenting with cystitis symptoms. Nitrofurantoin and fosfomycin appear to retain activity and remain effective for cystitis, including infections caused by MDR organisms. Therefore, these antibiotics may be considered for some patients with cystitis who are at risk for resistance. ▲

References are available at ContagionLive.com.

Additional risk factors for MDR cystitis include prior antimicrobial use, recurrent UTIs, and recent hospitalization, nursing home, or long-term care facility residence, among other things.
Although the incidence of HIV is declining, the prevalence of HIV infection and those living with the virus remains an issue. In the United States, approximately 1.1 million people are currently living with HIV/AIDS, and 38,739 new cases of HIV infection were reported in 2017.1,2 A majority of those cases are in men, aged 25 to 45 years, and men who have sex with men (MSM) and are disproportionately prevalent in communities of color, specifically black and African American. Worldwide, there are 1 million new sexually transmitted infections (STIs) daily.3 Sexuality, race, ethnicity, age, sex/gender identity, and geographic location have a direct impact on the risk of HIV acquisition.1,2

HIV PREVENTION: THE ACCESS ISSUE
Understanding an individual’s risk helps to make the right decision regarding HIV prevention strategies. Pre-exposure prophylaxis (PrEP) therapy includes taking an antiretroviral medication used in conjunction with harm reduction strategies to prevent HIV. PrEP is a vital component of the HIV care continuum that can help drastically reduce the number of new HIV infections.

Data from aidsvu.org reported that there were 77,000 HIV prevention users in 2016, which shows that for every 1 person with a new diagnosis, there were 2.5 HIV-negative people using PrEP.4 Unfortunately, those who can benefit most from PrEP care are not accessing therapy because of a variety of obstacles. Lack of provider education is a big barrier to PrEP care, with 1 in 3 primary care physicians and nurses reporting no knowledge of PrEP.5 A national online survey conducted in 2016 captured some of the reasons why one of the groups at highest risk (US MSM) was not accessing PrEP care by reviewing prescription data from community and mail-order pharmacies from September 2015 to August 2016. There were 4698 participants, of whom 85% had not used PrEP and 22% were unaware of PrEP. A majority of respondents (83%) reported at least 1 instance of condomless anal intercourse in the previous 3 months. The top reasons for not accessing PrEP care included cost (40.2%), concerns about potential adverse effects (31.4%), not knowing how to access PrEP care (30.6%), concerns about effects on insurance coverage (19.5%), and not suspecting a risk (19.3%), among others.6 These data show that PrEP therapy was not reaching a majority of those who could most benefit from care, specifically African Americans and Latinos.6 Of the estimated 500,000 PrEP-eligible African Americans, only 1% are receiving a prescription, and of the 300,000 PrEP-eligible Latino Americans, 3% received PrEP therapy.7 An alternative to a daily dosing strategy has been endorsed by the International Antiviral Society–USA Panel (IAS-USA) and the European AIDS Clinical Society (EACS) and could address some of these concerns and provide cost effectiveness, less toxicity, and easier access to regimens for individuals at high risk.7,8

CURRENT PREVENTION LANDSCAPE
Tenofovir disoproxil fumarate and emtricitabine (TDF/FTC; Truvada) is the first and only fixed-dose daily oral medication approved by the US Food and Drug Administration for prevention of HIV transmission.9 TDF/FTC was approved for use in adults as HIV prevention in July 2012, with its indication updated in 2018 to include daily dosing for adolescents ≥35 kg.9 The recommendations for daily PrEP therapy were initially published by the US Centers for Disease Control and Prevention in 2014 based on the favorable results of the iPrEx trial including MSM.10 Subsequent updates have included additional at-risk groups (heterosexuals/serodiscordant couples at high risk and people who inject drugs) and recommendations to help guide providers on how to best provide PrEP care. The most recent update to the guidelines by the CDC was in 2017. The success

The Case for On-Demand PrEP
What’s the 411 on 2-1-1?
BY CHRISTINA M. MADISON, PHARMD, FCCP, BCACP, AAHIVP, AND JOHN PHOENIX, APRN, FNP-C

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of this regimen based on clinical trial data was strongly correlated to adherence and identification of detectable levels of PrEP in the bloodstream or measurable levels in hair follicles.¹⁰

**EVIDENCE FOR ON-DEMAND PREP**

On-demand PrEP, also known as event-driven or pericoital PrEP, is HIV prevention based on planned intercourse and is taken only when needed, i.e., if a sexual encounter is with a person planned intercourse and is taken only when greater than 70% of the participants had detectable plasma drug levels of TFV. The efficacy determination by plasma blood levels of TFV was determined as the following: less than 2 doses per week (44%), to 2 to 3 doses per week (84%), 4 to 6 doses per week (100%), and 7 days per week (100%). Frequency of pill use was higher in the OLE, with 18 pills per month compared with 15 pills in the original trial.

**COST-BENEFIT ANALYSIS**

There are advantages and disadvantages of on-demand PrEP versus daily PrEP therapy. A few of the most notable advantages are decreased pill burden (fewer doses per month), fewer potential adverse effects as a result of less frequent dosing, and cost savings due to fewer pills consumed over time. The cost savings advantage is one of the most measurable specifically in MSM, who could most benefit from on-demand PrEP.¹¹ A new HIV infection can pose a significant financial burden. Infection can be averted through daily PrEP use, which is cost-efficient, but TDF/FTC 30 days per month for 12 months per year can still be expensive and is often a barrier to its use. This financial burden can be lessened with on-demand PrEP, based on the patient’s behavior and number of encounters. The Table¹⁴ shows the cost reduction based on the recommendations of event-driven PrEP and specifically the IPERGAY 2-1-1 regimen.

More data are needed for the CDC to fully endorse on-demand PrEP and add this option to its PrEP guidelines. Although, there are good efficacy data to support its use in specific individuals at high risk (MSM), based on those who may be taking very few doses and at less time prior to the sexual encounter, thus not allowing for adequate concentrations in affected tissues such as the rectum. This regimen has been endorsed by the IAS-USA and the EACS, and 2-1-1 dosing is listed in their guidelines. However, access to this medication and the cost factor could be affected by the availability of a generic equivalent to TDF/FTC in Europe. If on-demand PrEP were used in the United States, it would be considered an off-label use. The data currently support the use in MSM only, and there are no data to support its use in transgender men and cisgender women who engage in vaginal–penile intercourse because concentrations of TDF/FTC do not reach optimal levels in vaginal tissue within the on-demand PrEP timeline. PrEP therapy reaches maximum protection against HIV transmission through receptive anal intercourse after approximately 7 days of daily use compared with up to 20 days for receptive vaginal intercourse or injection drug use.⁷ On-demand PrEP should not be used in transgender women who are currently receiving gender-affirming care with feminizing hormones because of decreased concentrations of TFV¹²,¹⁶ The reduction in therapeutic concentrations means that only daily PrEP therapy should be recommended in this special situation for the most protection from HIV acquisition.¹⁵

Based on the data, on-demand PrEP should be considered a viable option for MSM who are at high risk, and it is one of many options in the toolbox for HIV prevention. PrEP use with TDF/FTC is only the beginning when it comes to chemoprophylaxis for HIV prevention, and additional options that take into consideration barriers to PrEP care are on the horizon, including an additional oral medication for PrEP (emtricitabine and tenofovir alafenamide [Descovy]). Data from the phase 3 DISCOVER trial were recently presented at the 2019 Conference on Retroviruses and Opportunistic Infections showing noninferiority to TDF/FTC, with improved safety regarding bone and renal health. There are multiple agents in the pipeline being investigated as prevention options in a variety of dosage forms and alternatives to daily oral therapy.⁷⁷ Addressing the knowledge gaps regarding HIV prevention options and the barriers to care will help those who are eligible for these life-changing therapies. Based on the data, on-demand PrEP is a reasonable alternative to daily PrEP and is highly effective for MSM with infrequent sexual exposure and planned sexual intercourse. ▲

**References available at ContagionLive.com.**

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**TABLE.** Cost Reduction Based on the Recommendations of Event-Driven PrEP¹⁴

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>POPULATION</th>
<th>MEDIAN DAYS PER WEEK HAVING SEX</th>
<th>PERCENTAGE OF COST ATTRIBUTED TO PREP DRUGS (%)</th>
<th>COST REDUCTION WITH EDD (%)</th>
<th>COST REDUCTION WITH TDD (%)</th>
<th>COST REDUCTION WITH IPERGAY REGIMEN (%)</th>
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<tr>
<td>United States</td>
<td>MSM (lower activity)</td>
<td>1</td>
<td>92-96</td>
<td>66-69</td>
<td>53-69</td>
<td>39-55</td>
</tr>
<tr>
<td>United States</td>
<td>MSM (higher activity)</td>
<td>1.5</td>
<td>92-96</td>
<td>39-69</td>
<td>39-69</td>
<td>0-55</td>
</tr>
<tr>
<td>France</td>
<td>MSM</td>
<td>1</td>
<td>96</td>
<td>69</td>
<td>55-69</td>
<td>41-55</td>
</tr>
<tr>
<td>Kenya</td>
<td>MSM</td>
<td>1</td>
<td>21</td>
<td>15</td>
<td>12-15</td>
<td>9-12</td>
</tr>
<tr>
<td>South Africa</td>
<td>Heterosexual (lower activity)</td>
<td>1</td>
<td>47-53</td>
<td>34-38</td>
<td>27-38</td>
<td>20-30</td>
</tr>
<tr>
<td>South Africa</td>
<td>Heterosexual (higher activity)</td>
<td>2</td>
<td>47-53</td>
<td>20-30</td>
<td>20-30</td>
<td>0-23</td>
</tr>
</tbody>
</table>

EDD indicates event-driven pre-exposure prophylaxis; IPERGAY, Préventive de l’Exposition aux Risques avec et pour les Gays; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDD, time-driven pre-exposure prophylaxis (regimens from HPTN 067/ADAPT).
Vancomycin remains an impressive workhorse in the MRSA treatment landscape; however, its utility is limited by slow bactericidal activity, evolving dosing strategies that necessitate labor-intensive therapeutic drug monitoring, nephrotoxicity, and suboptimal clinical outcomes data despite decades of use. Daptomycin is an alternative first-line agent for the treatment of MRSA bacteremia and is associated with less nephrotoxicity and more convenient dosing strategies compared with vancomycin. Nonetheless, the outcomes of patients treated with standard daptomycin doses are underwhelming, as only 44% of patients with MRSA bacteremia achieved clinical success following receipt of a 6-mg/kg daily dose.1 Of concern, gene mutations that confer daptomycin tolerance and enhanced S. aureus survival have been reported.2,3 Unlike treatment with vancomycin, higher doses of daptomycin (ie, ≥8 mg/kg/day) demonstrate more rapid in vitro killing and suppression of resistance and are associated with improved clinical outcomes.4,5

An alternative approach is combination therapy with a β-lactam, which offers similar advantages as high-dose daptomycin but may allow for use of lower vancomycin or daptomycin doses.4 Historically, combination approaches have been employed for treatment-refractory or persistent MRSA bacteremia; however, new data indicate that such approaches could have benefit if employed much earlier.

The Infectious Diseases Society of America clinical practice guidelines for the treatment of MRSA infections recommend high-dose daptomycin (ie, 10 mg/kg/day) in combination with another antibiotic as salvage therapy for persistent MRSA bacteremia and/or vancomycin treatment failures.7 Unfortunately, there are minimal data to demonstrate which antibiotic combinations are preferred or when combination therapy should be initiated or stopped. Moreover, the role of novel MRSA-active antibiotics is not represented, as the guidelines were published only months after ceftaroline received approval from the US Food and Drug Administration and years before even newer agents were introduced on the market. Interestingly, patients often receive empiric “combination therapy” in clinical practice with vancomycin plus either cefepime or piperacillin-tazobactam. Recent data suggest that patients receiving at least 24 hours of cefepime have improved clearance of MRSA bloodstream infections compared with patients receiving vancomycin monotherapy, and this may be a preferred empiric regimen if cefepime has adequate in vitro activity against gram-negative nosocomial pathogens within the institution.8

β-Lactam antibiotics are likely the preferred partner agents for vancomycin and daptomycin because of their enhanced safety compared with other antibiotic classes that may be considered for synergy and because of the favorable economic profile of older β-lactam agents such as cefazolin. The absence
of real-world clinical data for the use of novel MRSA-active agents for complicated infections, taken with compelling in vitro synergy data and desire to use antibiotics judiciously, warrants the investigation of β-lactam combination therapies. Briefly, we review the available in vitro and clinical data for β-lactam combination therapies in the treatment of MRSA bacteremia.

**IN VITRO DATA**
Several mechanisms of synergy exist between β-lactams and vancomycin or daptomycin. Notably, increasing glycopeptide resistance is associated with improved susceptibility to β-lactam antibiotics through a phenomenon called the seesaw effect. Possible explanations include increased expression of penicillin-binding protein (PBP) 2, decreased PBP4, and/or inactivation of the meca gene in vancomycin-intermediate *S aureus* (VISA) or vancomycin-resistant strains. Among the 4 PBPs produced by *S aureus*, PRP1 blockade is most strongly associated with daptomycin potentiation. Therefore, β-lactams with affinity for PPB1 (eg, ceftriaxone, nafcillin, meropenem) enhance anti-MRSA activity of daptomycin, whereas those with minimal affinity (eg, ceftriaxone, cefoxitin) do not. Interestingly, ceftaroline is more active against MRSA isolates with higher vancomycin and daptomycin minimum inhibitory concentrations because of enhanced PB2 binding. Other bacterial genetic and metabolic adoptions may confer changes to the bacterial cell wall. Indeed, ceftaroline enhances daptomycin-induced cell membrane depolarization and reduces cell wall thickness of both daptomycin-susceptible and -resistant strains of *S aureus*, including biofilm-producing MRSA. This potent synergy may result in clinical de-escalation or sparing of higher daptomycin doses.

Synergy may also be explained by immune system regulation. Sakoulas and colleagues found that exposure to nafcillin significantly increased the activity of host defense peptides, particularly human cathelicidin LL-37, against *S aureus*, resulting in enhanced killing. The effect was more pronounced at higher doses; however, synergistic effects were observed at extremely low nafcillin concentrations. Importantly, the effect was also observed with ampicillin, piperacillin, cefazolin, cefoxitin, and ceftaroline. The combinations of vancomycin and cefazolin, cefepime, ceftaroline, and nafcillin all demonstrated improved in vitro killing against vancomycin-susceptible, heterogeneous VISA, as well as VISA strains, compared with vancomycin alone.

**CLINICAL DATA**
Retrospective analyses of patients receiving vancomycin or daptomycin plus a β-lactam show shorter durations of bacteremia but no impact on rates of clinical failure compared with monotherapy. Notably, however, bacteremia persisted for a median of 10 days prior to combination therapy initiation in these studies. Indeed, ceftaroline has been used successfully with vancomycin and daptomycin as salvage therapy for patients with refractory, persistent MRSA bacteremia. Ceftaroline is an attractive choice to use in combination because it is the only β-lactam with in vitro activity against MRSA in addition to the synergistic laboratory effects previously described. The question of whether ceftaroline monotherapy would demonstrate improved clinical outcomes compared with vancomycin or daptomycin monotherapy or combination regimens remains unanswered.

Patients are more likely to benefit from combination therapy earlier in the treatment course, particularly patients at higher risk of mortality. A retrospective evaluation of 171 patients with MRSA bacteremia found mortality was reduced by 80% at 60 days for patients with a primary endovascular source receiving combination therapy with daptomycin plus ceftaroline within 72 hours of index blood culture. In a recent prospective trial, patients with MRSA bacteremia were randomized to daptomycin (6-8 mg/kg/day) plus ceftaroline (600 mg every 8 hours) or standard monotherapy within 72 hours. No patients (0 of 17) in the combination therapy arm died compared with 26% (6 of 23) of patients in the standard therapy arm, resulting in early termination of the study. All deaths were among patients with an endovascular source and the majority (5 of 6) had serum IL-10 concentrations >5 pg/mL. The median duration of combination therapy was 8 days before de-escalation to monotherapy, which is notable because evidence to support the duration of combination therapy is lacking. Short durations of early combination followed by definitive monotherapy may be economically advantageous and spare unnecessary antibiotic exposures and toxicities.

An earlier prospective clinical trial that evaluated β-lactam combination therapy for MRSA bacteremia enrolled 60 patients who were randomly assigned to receive vancomycin or vancomycin plus flucloxacillin for 7 days within 48 hours of the first positive blood culture. Patients receiving combination therapy had a 24-hour shorter duration of bacteremia, and fewer patients experienced persistent bacteremia. No difference in mortality was observed, owing to the small sample size. A subsequent open-label trial (NCT02365493) of adult patients with MRSA bacteremia was designed to further elucidate the clinical effectiveness of early combination therapy based on these data. Patients were randomized within 72 hours of the first positive blood culture to either standard therapy (vancomycin or daptomycin monotherapy) or combination therapy with vancomycin or daptomycin plus 7 days of an antistaphylococcal β-lactam (flucloxacillin, cloxacillin, or cefazolin). The primary outcome is a composite measure of all-cause mortality, persistent bacteremia at 5 days or greater, microbiological relapse (defined as a MRSA-positive blood culture at least 72 hours after a negative culture), and microbiological treatment failure (defined as MRSA isolated from any sterile site except urine at least 14 days after randomization). The trial closed enrollment in December 2018 per the study protocols.

**CONCLUSIONS**
Based on available and emerging data, it is reasonable to employ combination therapy with a PB1-active β-lactam or ceftaroline early in the MRSA bacteremia treatment course, particularly in patients at the highest risk of treatment failure or death. Seven days of combination therapy may be sufficient if employed early in the treatment course, but more clinical data are needed to determine the optimal drug pairings and duration of combination therapy. Empiric monotherapy with ceftaroline compared with vancomycin or daptomycin monotherapy or combination regimens needs to be explored.

References are available at ContagionLive.com.
Future of Fluoroquinolones: Risks, Benefits of Antibiotic Workhorse

Warnings and concerns regarding fluoroquinolones are on the rise, but the antibiotics still play a role, albeit more limited, in the treatment of various infectious diseases.

BY LUCIA ROSE, PHARMD, BCIDP, AND MADELINE KING, PHARMD, BCIDP

(continued from cover page)

because the risks of adverse effects (AEs) of FQs outweigh the potential benefits. A 21-member FDA advisory panel convened in November 2015 to discuss FQ use for common infectious indications. The overall consensus was to avoid FQs for acute bacterial sinusitis, acute chronic obstructive pulmonary disease exacerbations, and uncomplicated urinary tract infections unless no alternative treatments exist.1 For these diseases, there are other effective options that are considered safer and to have less propensity for collateral damage.2

Current FDA boxed warnings for the FQ class include myasthenia gravis (MG) exacerbation as well as serious adverse reactions, including effects on the central nervous system (CNS), tendinitis, tendon rupture, and peripheral neuropathy.1,3 FQs can also result in corrected QT prolongation with a risk, albeit low, of torsade de pointes. Other recent warnings from the FDA have included glucose homeostasis disturbances and a risk of aortic aneurysm and aortic dissection.4,5

The proposed mechanisms by which FQs can exacerbate MG include alteration of neural transmission at neuromuscular junctions and FQ chelation of calcium, which inhibits acetylcholine release presynaptically. A literature search of the FDA Adverse Event Reporting System database in 2011 found 37 reported cases, with a median of 1 day from the start of FQ therapy to exacerbation of MG symptoms. Dyspnea was reported as the most common symptom of the exacerbation.6 It seems prudent to avoid FQs in patients with MG despite lack of concrete evidence of the mechanism of exacerbation induction.

FQs affect the CNS by their actions on GABA_A and N-methyl-D-aspartate receptors and can result in attention disturbance, disorientation, agitation, nervousness, memory impairment, delirium, and seizures. These effects may be worsened if there is poor renal function, resulting in higher serum concentrations of the drugs, or if the blood–brain barrier is compromised in any way.7 The risk of tendinitis and tendon rupture has been demonstrated in several studies and was first reported in 1983. These effects most often occur in the Achilles tendon and are more of a concern for patients over 60 years and those with poor renal function. The mechanism is likely due to alterations in collagen formation.8,9 Patients taking FQs should be counseled to avoid rigorous physical activity to reduce their risk of tendon-related AEs.

A recently recognized AE of FQs is aortic aneurysm and dissection. A study in Denmark compared a cohort of patients who received FQ antibiotics over a 7-year period with a control group who received amoxicillin. The investigators

LUCIA ROSE, PHARMD, BCIDP

Rose received a PharmD at Massachusetts College of Pharmacy & Health Sciences, completed a PGY-1 pharmacy practice residency at UMass Memorial Health Care, and a PGY-2 infectious diseases pharmacotherapy residency at The Brooklyn Hospital Center. She is currently the co-director of the Antimicrobial Stewardship Program at Cooper University Hospital in Camden, New Jersey, and is as an adjunct professor at Cooper Medical School of Rowan University and University of the Sciences.
It is possible that not all providers have received the negative and serum levels, lack of cross-reactivity in patients with a likely due to the ease of dosing, adequate tissue penetration with moxifloxacin. Currently available FQs, the risk appears to be highest Escherichia coli has been shown to be linked with prior FQ usage. A recent lence of FQ resistance if they had used FQs, as did those in their geographic area. Patients had an increased prevalence of FQ resistance if they had used FQs, as did those in the same neighborhoods with higher FQ use.2 Despite warnings, providers still commonly prescribe FQs as first-line treatment for many uncomplicated indications. In fact, FQs are the fourth-most commonly prescribed antibiotic class in the United States; in 2014, 32.8 million prescriptions for FQs were issued.13 Unnecessary overuse is likely due to the ease of dosing, adequate tissue penetration and serum levels, lack of cross-reactivity in patients with a β-lactam allergy, and years of experience with these agents. It is possible that not all providers have received the negative

messages. Caution should be taken when prescribing FQ antibiotics, especially to elderly patients and those with poor renal function, although not all AEs are correlated with higher serum concentrations. Also, many AEs have been reported to occur early in treatment, indicating that even short courses may be harmful.

Nevertheless, FQs certainly continue to play an important role, particularly for severe infections due to GN bacteria, including pyelonephritis, bacteremia, biliary tract or intra-abdominal infections, pneumonia, bone and joint infections, endocarditis, and even CNS infections. Risks of FQ toxicity may be outweighed by the benefit of FQs’ high oral bioavailability, allowing patients with functioning gastrointestinal tracts to receive an oral therapy. Many of these patients would otherwise need intravenous antibiotics administered via a peripherally inserted central catheter line or other longer-term venous access. Two important recently published studies, one on infective endocarditis and the other on bone and joint infections, both incorporated a number of oral FQs for many of the antibiotic regimens because of their pharmacokinetic properties.14,15

Lastly, a growing body of evidence is available to support shorter antibiotic durations for many GN infections, therefore limiting the time of exposure and vulnerability to FQ-induced toxicity. The Table describes 3 important studies evaluating primarily GN infections that support shorter durations of therapy.

To preserve the utility of these agents and keep patients safe, institutions should restrict FQ use to appropriate indications, and outpatient providers should be held accountable for unnecessarily prescribing this class of antibiotics. FQs are a highly valuable antibiotic class, but because of concerns for resistance and AEs, they should be reserved for compelling indications, particularly when safer and equally effective alternatives exist. ▲

References are available online at ContagionLive.com.

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<th>POPULATION</th>
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<tr>
<td>Sandberg T et al. Lancet. 2012;380(9840): 484-490.14</td>
<td>248 adult, nonpregnant women with acute pyelonephritis</td>
<td>Prospective, randomized, noninferiority trial comparing oral ciprofloxacin 500 mg twice daily for 7 vs 14 days</td>
<td>Seven vs 14 days was noninferior for treatment of pyelonephritis in nonpregnant women.</td>
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<tr>
<td>Sawyer RG et al. N Engl J Med. 2015;372(21):1996-2005.17</td>
<td>518 adult patients with complicated intra-abdominal infections</td>
<td>Prospective, randomized trial comparing 4 days after source control vs traditional strategy</td>
<td>Four days after successful source control was equivalent to traditional duration of treatment until resolution of signs/symptoms.</td>
</tr>
<tr>
<td>Yahav D et al. Clin Infect Dis. Published online December 11, 2018.18</td>
<td>604 adult patients with GN bacteremia</td>
<td>Prospective, randomized, noninferiority trial comparing 7 vs 14 days for GN bacteremia (mostly urinary source)</td>
<td>Seven vs 14 days was noninferior for patients with uncomplicated GN bacteremia.</td>
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</table>

FQ indicates fluoroquinolone; GN, gram-negative.
Health care professionals can use Twitter as a means to educate the general public, connect with other experts in the medical community, and increase access to principles of antibiotic stewardship in countries with limited resources. However, establishing a professional platform on Twitter can be challenging, said Debra Goff, PharmD, and John Nosta, BA, in a recent Contagion® Peer Exchange panel.

The panelists discussed tips for writing headlines for tweets, using hashtags to connect with an audience or a topic, and selecting active Twitter users who have a relevant target audience for a particular tweet. Goff and Nosta concluded the panel with a brief overview of the benefits of Twitter chats for dispelling false information about health topics.

**PERSONAL AND PROFESSIONAL CONNECTIONS**

In addition to educating the medical community and the general public about antibiotic stewardship, Twitter can foster the development of personal relationships among medical professionals, according to Goff and Nosta. Goff described a personal experience in which she met 2 of her Twitter connections (John Alverdy, MD, head of surgery, and Gary An, MD, general surgeon, both of the University of Chicago) when they were caring for one of her family members. After this in-person meeting, Alverdy invited Goff to spend a day educating members of the University of Chicago surgical department about antibiotic stewardship, and Goff later invited him to be a keynote speaker at a meeting at The Ohio State University (Goff’s institution).

“It was so comforting because our family member was very sick...and all of a sudden, there was this different connection because we followed each other on Twitter,” said Goff.

**COMMUNICATION AND EDUCATION AROUND THE WORLD**

Twitter can also bring information about antibiotic stewardship to countries with limited resources. Goff discussed the mentoring program that she had started to teach medical professionals in South Africa how to use Twitter to connect with experts around the world.

“We’re connecting people within the continent of Africa [with] stewardship,” said Goff. “I have people from Rwanda starting to connect with me, and [I tell them to] plug into the South African network. [Twitter is] really an amazing vehicle.”

Goff added that many low- and middle-income countries in Africa have limited access to journals outside their country. “They’re not seeing what the rest of the world is seeing,” she said. “Twitter removes those barriers.”

**TIPS FOR MEDICAL PROFESSIONALS ON USING TWITTER**

Nosta noted that becoming comfortable with Twitter for professional purposes can be daunting for health care practitioners who have little experience with social media. He emphasized the importance of an engaging, “sticky” headline for a tweet to help catch the attention of his followers. He usually includes a link, he said, but he emphasized the importance of checking the link before sending the tweet because the article could include incorrect information, originate from an unreliable source, or be outdated.
“[The headline has] got to be resonant,” Nosta said. “Oftentimes I’m tweeting a link…but I don’t use that headline [that populates the Twitter feed after clicking the tweet tab]. I look at it, and I change it. I make it shorter.”

Nosta and Goff also discussed the importance of including hashtags in a tweet to connect with an audience or a topic and maximize the number of users who see the tweet. Goff said that almost all her tweets have the hashtag #antibiotics, and Nosta stated that most of his tweets include the hashtag #healthtech or #digitalhealth to attract his audience.

“Sometimes I’ll do a tweet on Elon Musk’s driverless car, but I’ll put in #digitalhealth because it shares perhaps an intellectual or emotional border that makes my feed a little bit more interesting,” said Nosta. “Social media to me is 20% media [and] 80% social.”

Goff added that she sometimes includes a #surgeons hashtag when she posts articles from infectious disease journals not typically read by surgeons to call their attention to relevant topics for their practice, such as surgical site infections and outcomes with a new antibiotic. She also tags key surgical influencers, such as Alverdy; Chris Ellison, MD, head of surgery at The Ohio State University; and Ben Nwomeh, MD, pediatric surgeon at The Ohio State University, and has lists of surgeons in different specialties to whom she directly tweets articles.

“When I see articles relevant to a critical care physician, I’m tweeting it right to [the president of the Society of Critical Care Medicine], and I know he or she will disseminate that throughout,” Goff said. “If I tweet something with #sidpharm [Society of Infectious Diseases Pharmacists], I know it’s going to go out to all infectious disease pharmacists, and that’s the audience I’m trying to meet. Knowing your audience helps you understand how to disseminate your message rapidly.”

Goff and Nosta also emphasized the value of having a link or a picture connected to the article or the topic. Nosta said that sometimes the visual element of his tweet is as simple as a screenshot of a paragraph in the article. “We underestimate the power of the visual,” he noted. “Sometimes I’ll even just grab a picture to put into my tweet. But a really good bar chart or really good pie chart that shows the distribution of a pathogen in a particular disease could be really powerful.”

Goff added that health care professionals need to use Twitter responsibly, as their tweets are a direct reflection of them and the institution they work at. “Someone is following every tweet you send,” she said. “I always assume my university [is] monitoring my tweets. I see [tweeting] as an extension of representing my university in a very positive way because I’m reaching a whole different audience than [they are] because I’m the health care provider, I’m not the university or the hospital, so it’s really a win-win because they can then promote my tweets and they have a different circle of followers than I do.”

**TWITTER CHATS**

Goff and Nosta concluded their discussion with an overview of how Twitter chats (scheduled, topical conversations that revolve around a specific hashtag) connect the community with medical experts around the world. For example, the Antibiotic Stewardship Program chat (available to Twitter users by searching #aspchat) was a focused Twitter discussion that included content experts posting questions.

“You could be a patient affected by MRSA [methicillin-resistant *Staphylococcus aureus*], and now you have direct access to world leaders answering questions,” said Goff, although she added that professionals are careful to avoid giving medical advice publicly over Twitter.

Goff also pointed out that the hashtag helps to catalyze the conversation and provide data to counter consumer groups that provide false information about health care issues, such as antivaccine groups. “I see how vaccines save lives, but there are a lot of people who don’t believe in them, and they have a large presence on social media,” she said. “If not us, then who to dispute that with medical facts? You really need to have a balance of both so you can have medical factual data from the people who see the consequences of people not being vaccinated.” ▲

**TIPS FOR MEDICAL PROFESSIONALS ON TWITTER**

1. Grab the reader with a “sticky” headline.
2. Check your links.
3. Maximize reach with hashtags.
4. Tag key opinion leaders.
5. Know your audience.
6. Integrate visual elements.
7. Participate in Twitter chats.
Warnings and precautions (cont’d)

Comprehensive risk reduction strategies

• Reduce HIV-1 risk: TRUVADA FOR PrEP is not always effective in preventing HIV-1. Use only as part of a comprehensive prevention strategy that includes safer sex practices, regular testing for HIV-1 and other STIs, and counseling on reducing sexual risk behaviors.

• Reduce potential for drug resistance: TRUVADA FOR PrEP should only be used in individuals confirmed to be HIV-negative immediately prior to initiation, at least every 3 months while taking TRUVADA, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA. TRUVADA alone is not a complete regimen for treating HIV-1.

• HIV antibody tests may not detect acute HIV infection. If recent exposures are suspected or symptoms of acute HIV infection are present (e.g., fever, fatigue, myalgia, skin rash), delay initiating (≥1 month) or discontinue use and confirm HIV-negative status with a test approved by the FDA for the diagnosis of acute HIV infection.

• If a screening test indicates possible HIV-1 infection, convert the HIV-1 PrEP regimen to an HIV treatment regimen until HIV-negative status is confirmed.

• Counsel on adherence: Counsel individuals to strictly adhere to their dosing schedule, as efficacy is strongly correlated with adherence. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

Adverse reactions

• Common adverse reactions (≥2% and more frequently than placebo) of TRUVADA FOR PrEP in clinical trials were headache, abdominal pain, and weight loss.

Drug interactions

• Prescribing information: Consult the full Prescribing Information for TRUVADA FOR PrEP. Drug interactions, including clinical comments.

Hepatitis C antivirals: Coadministration with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir increases TDF exposure; monitor for adverse reactions.

• Drugs affecting renal function: Coadministration of TRUVADA with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of emtricitabine and/or tenofovir.

Pregnancy and lactation

• Pregnancy: An Antiretroviral Pregnancy Registry (APR) has been established. Available data from observational studies and the APR show no increase in the rate of major birth defects for TRUVADA compared with a US reference population. Consider HIV prevention methods, including TRUVADA FOR PrEP in women due to the potential increased risk of HIV-1 infection during pregnancy and mother to child transmission during acute HIV-1 infection.

• Lactation: Emtricitabine and tenofovir have been detected in human milk. Evaluate the benefits and risks of TRUVADA FOR PrEP in breastfeeding women, including the risk of HIV-1 acquisition due to nonadherence, and subsequent mother to child transmission. Health benefits of breastfeeding should be considered along with potential adverse effects of TRUVADA on the child, which are unknown.

Dosage and administration

• Dosage: One tablet once daily with or without food.

• HIV screening: Test for HIV-1 infection prior to initiating and at least every 3 months during treatment.

• HIV screening: Test for HBV infection prior to or when initiating treatment.

• Renal impairment and monitoring: Not recommended in individuals with CrCl <60 mL/min. In all patients, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus.

TRUVADA FOR PrEP (pre-exposure prophylaxis) is indicated to reduce the risk of sexually acquired HIV-1 in adults and adolescents (≥15 kg) who are at risk for HIV, when used in combination with safer sex practices. HIV-negative status must be confirmed immediately prior to initiation.

- If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiation for at least 1 month until HIV-negative status is reconfirmed. Alternatively, confirm HIV-negative status with a test cleared by the FDA to aid in the diagnosis of acute HIV-1 infection.

Individuals at risk for sexually acquired HIV-1 may include those:

- With HIV-1 infected partner(s), or
- Who engage in sexual activity in a high prevalence area or social network and have additional risk factors, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities, use of illicit drugs or alcohol dependence, incarceration, or sexual partners of unknown HIV status with any of these risk factors.

**IMPORTANT SAFETY INFORMATION**

boxed warning: Risk of drug resistance with use of Truvada for PrEP in undiagnosed early HIV-1 infection and post treatment acute exacerbation of hepatitis B

- TRUVADA FOR PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of TRUVADA FOR PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed.
- Severe acute exacerbations of hepatitis B have been reported in HBV-infected patients who discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients with HBV after discontinuing TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

**Contraindications**

- Do not use TRUVADA FOR PrEP in individuals with unknown or positive HIV status.

TRUVADA FOR PrEP has a Risk Evaluation and Mitigation Strategy (REMS). For further information, visit www.ftc-tdf-preprems.com.

Please see Brief Summary of full prescribing information on the following page.
TRUVADA® (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PRE-EXPOSURE PROPHYLAXIS (PREP) IN UNDIAGNOSED EARLY HIV-1 INFECTION AND POST-TREATMENT ACUTE EXACERBATION OF HIV-1 INFECTION

TRUVADA for PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV variants have been identified with use of TRUVADA for PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for PrEP if signs or symptoms of acute HIV-1 infection are present unless negative HIV status is confirmed.

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued TRUVADA. Hepatitis B should be monitored closely in HBV-infected patients who discontinue TRUVADA. If appropriate, initiation of anti-HBV therapy may be warranted.

INDICATIONS AND USAGE: [See Dosage and Administration]

TRUVADA for PrEP (pre-exposure prophylaxis) is indicated to reduce the risk of sexually acquired HIV-1 in adults and adolescents (weighing at least 35kg) who are at risk for HIV, when used in combination with safer sex practices. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for PrEP.

• If clinical symptoms of acute HIV-1 infection are present and recent exposures (<1 month) are suspected, delay initiation for at least 1 month until HIV-negative status is reconfirmed. Alternatively, confirm HIV-negative status with a test cleared by the FDA to aid in the diagnosis of acute HIV-1 infection.

Individuals at risk for sexually acquired HIV-1 may include those:
- With partner(s) known to be HIV-infected, or
- Who engage in sexual activity within a high prevalence area or social network and have additional risk factors, such as: inconsistent or no condom use, diagnosis of sexually transmitted infections (STIs), exchange of sex for commodities (such as money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, or sex with partner(s) of unknown HIV-1 status with any of the factors listed above.

DOSE AND ADMINISTRATION: [See Indications and Usage, Contraindications, and Warnings and Precautions]

HIV-1 Screening: Screen all patients for HIV-1 infection before initiating TRUVADA for PrEP and at least once every 3 months while taking TRUVADA.

Testing Prior to Initiation and During Use: Prior to or when initiating TRUVADA, test patients for hepatitis B infection.

Prior to initiation and during use of TRUVADA, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance (Ccr), urinalysis, uric acid, blood glucose, and liver function tests in all patients with chronic liver disease, also assess serum phosphorus. TRUVADA for PrEP is not recommended in individuals with a Ccr <60 mL/min. If a decrease in Ccr is observed, evaluate potential causes and re-assess potential risks and benefits of continued use.

Bone Loss and Mineralization Defects: [See Adverse Reactions]

Bone mineral density (BMD) in clinical trials in HIV-infected adults, TDF was associated with decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to controls. Serum parathyroid hormone levels and 1,25 vitamin D levels were also higher in subjects receiving TDF. In clinical trials in HIV-infected subjects aged 2 to <18 years, bone effects were less pronounced than those observed in adults and suggested a decrease in bone turnover. Total body BMD gain was less in TDF-treated HIV-infected pediatric subjects as compared to the control group; skeletal growth (height) appeared to be unaffected. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Consider assessing BMD in adults and adolescents with a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be considered in individuals at risk. Additional supportive care, such as appropriate consultation should be obtained. Mineralization defects. Cases of osteomalacia associated with proximal renal tubulopathy, manifesting as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF. Anhidrosis and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia in children with chronic kidney disease may lead to possible clinically significant adverse reactions from concomitant drugs. Consider the potential for increased exposures of concomitant drugs. Consider the potential for increased exposures of concomitant drugs.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). In patients with chronic kidney disease, also assess serum phosphorus. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high doses of multiple NSAIDs). Treatments for acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on two or more antiretroviral drugs. Treatment with TRUVADA and hospitalization or renal replacement therapy. Alternatives to NSAIDs should be considered in patients at risk for renal dysfunction. Persistent or worsening bone pain, pain in extremities, fractures and/or muscle pain or osteomalacia secondary to proximal renal tubulopathy should prompt a discontinuation of TRUVADA for PrEP in adults and adolescents. Consider the potential for increased exposures of concomitant drugs.

WARNING: RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PREREVENTION (PREP) IN HIV-1 INFECTED INDIVIDUALS: [See Warnings and Precautions]

TRUVADA was similar to that observed in adults. The median duration of exposure in PrEP clinical trials were headache, abdominal pain, and decreased appetite. In adult patients, treatment with TRUVADA led to a decrease in renal function in some patients, primarily in those with pre-existing renal impairment. Consider potential increased risk of HIV-1 infection during pregnancy and postpartum in women who initiate or discontinue TRUVADA during pregnancy. Consider the potential for fetal harm when TRUVADA is used during pregnancy and protect against potential risks and benefits of continued use.

Bone Mineral Density: iPrEx: Decreases in BMD were observed in a substudy of 503 HIV-1 uninfected adults. Mean changes from baseline in BMD ranged from -0.4% to -1% across total hip, femoral neck, and trochanter, which returned toward baseline after discontinuation of TRUVADA. Seventeen percent of subjects receiving TRUVADA for PrEP lost >5% of spine BMD during treatment and 1.7% of subjects lost >20% bone mineral density (BMD) at the total spine. BMD was not evaluated in this trial; however, fracture rates were similar between treatment and placebo groups (0.8% vs 0.6%, respectively). ATN113: in the TRUVADA arm of iPrEx discontinued due to an increase in BMD loss Week 48 (+2.5+ for lumbar spine and +0.2 for total body). One subject had significant (<4%) total body BMD loss at Week 24 and 3 subjects showed a worsening (change from >-2 to <) in their lumbar spine or total body BMD Z-scores at Week 24 or 48. Interpretation of these BMD data in adolescents may be limited by the low rate of adherence to TRUVADA by Week 48.

Consult the full Prescribing Information for TRUVADA for additional information regarding adverse reactions, laboratory abnormalities, and postmarketing events when used for another indication.

DRUG INTERACTIONS: [See Warnings and Precautions]

Hepatitis C antiviral agents: Coadministration with ledipasvir/sofosbuvir, velpatasvir/sofosbuvir, or sofosbuvir/velpatasvir increases tenofovir exposure, monitor for adverse reactions associated with TDF.

Dysfunction: Reticular (FTC) and tenofovir are primarily eliminated by the kidneys through a combination of glomerular filtration and active tubular secretion. No drug interactions due to competition for renal excretion have been observed; however, combination therapy with TRUVADA with drugs that compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or the coadministered drugs, which may increase the incidence or severity of adverse reactions.

USE IN SPECIFIC POPULATIONS: [See Dosage and Administration and Adverse Reactions]

Pregnancy: Pregnancy Exposure Registry (APR): A pregnancy exposure registry has been established to monitor pregnancy outcomes in women exposed to TRUVADA. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. Risk Summary: Available data from observational studies and the APR show no increase in the rate of major birth defects for TRUVADA compared with a US reference population. Consider HIV prevention methods, including TRUVADA for PrEP in at-risk women due to the potential increased risk of HIV-1 infection during pregnancy and postpartum in women who initiate or discontinue TRUVADA during acute HIV-1 infection. Lactation: Emtricitabine and tenofovir have been detected in human breast milk. Evaluate the benefits and risks of TRUVADA for PrEP in breastfeeding women, including the risk of HIV-1 acquisition due to nonadherence, and subsequent mother to child transmission. Health benefits of breastfeeding should be considered along with potential adverse effects of TRUVADA on the child, which are unknown. Pediatric Use: The safety and effectiveness of TRUVADA for PrEP in adolescents (weighing at least 35kg) is supported by data from clinical studies conducted in adults. Additional supporting data was obtained from safety and pharmacokinetic studies conducted with individual drug products, FTC and TDF, in HIV-infected adults and pediatric subjects. Safety, adherence, and resistance were evaluated in adolescents in study ATN113. The safety profile of TRUVADA was similar to that observed in adults. In the 52-week study drug discontinuations markedly after adolescents were switched from monthly to quarterly visits, suggesting that adolescents may benefit from more frequent visits for monitoring. In the ATN113 PrEP trial, TRUVADA for PrEP is not recommended in HIV-infected individuals with Ccr below 60mL/min. If a decrease in estimated Ccr is observed, while using TRUVADA, assess potential causes and re-assess potential risks and benefits of continued use.

OVERDOSAGE: If overdose occurs, the patient must be monitored for evidence of toxicity and administered standard supportive treatment as necessary.

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Rezafungin is a new echinocandin being developed for the treatment and prevention of fungal infections in allogenic hematopoietic stem cell transplant (HSCT) recipients and other patients at high risk of infection. The pharmacokinetics of rezafungin allow for once-weekly dosing. Several in vitro studies identified possible interactions in which the risk of drug–drug interactions (DDIs) could not be ruled out relative to the 400-mg once-weekly dose of rezafungin. As a result, investigators from manufacturer Cidara Therapeutics conducted clinical in vivo evaluations of drug interaction potential.

“Many current drugs used in this patient population are known to interact with other antifungal agents through metabolic enzymes and transporter pathways, causing drug levels to be too high [leading to toxicity] or too low [leading to decreased efficacy],” Taylor Sandison, MD, MPH, chief medical officer of Cidara and an investigator on the study, told Contagion®. “Azole antifungals, which are the most common antifungal used for IFD [invasive fungal disease] prophylaxis, are well known for causing these types of drug–drug interactions, primarily through cytochrome P450 [CYP] enzyme metabolism.”

For the open-label inpatient study, the investigators followed 26 healthy participants to evaluate DDIs between rezafungin and probe drugs with known interactions with CYP enzymes and transporters as well as drugs likely to be coadministered with rezafungin.

“The DDI study is meant to inform study sites about potential drug–drug interactions with rezafungin by measuring serum levels of specific drugs that use these CYP and transporter pathways when they are administered alone and then administered with rezafungin,” Sandison said.

Each participant received a loading dose of 600 mg of rezafungin on the first dosing day, followed by 400-mg doses on days 10 and 15. The probe drugs were administered as part of a cocktail containing at least 2 drugs, once prior to and once after receiving rezafungin on a schedule allowing for washout between doses and limiting interactions with other drugs.

“Samples were analyzed to determine RZF [rezafungin], tacrolimus, repaglinide, metformin, rosuvastatin, pitavastatin, caffeine, efavirenz, midazolam, and digoxin concentrations in plasma (except for tacrolimus, which was in whole blood) to characterize the PK [pharmacokinetics] profile of each analyte,” the investigators wrote, noting that pharmacokinetic exposure parameters were calculated from the plasma concentration time profiles by noncompartmental analysis.

The investigators found that no relevant change in systemic concentrations of the probe drugs was observed when rezafungin was dosed concomitantly with metformin, pitavastatin, caffeine, efavirenz, midazolam, digoxin, tacrolimus, repaglinide, and rosuvastatin. Pharmacokinetic exposure of all drugs was similar with or without rezafungin, providing evidence that no dose adjustment should be expected when rezafungin is coadministered with these commonly used drugs.

“Our global, phase 3 ReSTORE clinical trial of rezafungin for the treatment of candidemia and invasive candidiasis is moving forward, and patient enrollment is under way. We also continue to plan for initiation of the phase 3 ReSPECT prophylaxis clinical trial of rezafungin in patients undergoing allogenic blood and marrow transplantation,” Sandison said.

The study, “No Relevant Pharmacokinetic (PK) Interaction Between Rezafungin and Nine Probe Drugs: Results From a Drug-Drug Interaction (DDI) Study,” was presented February 23, 2019, at the Transplantation & Cellular Therapy (TCT) Meetings of the American Society of Blood and Marrow Transplantation and the Center for International Blood & Marrow Transplant Research in Houston, Texas. ▲

Reference is available at ContagionLive.com.
ATLAS: Long-Acting Injectable Noninferior to Oral ART at 48 Weeks

BY CONTAGION® EDITORIAL STAFF

The 48-week results of the ATLAS study indicate that the regimen of monthly injectable cabotegravir/rilpivirine is noninferior to continued 3-drug oral antiretroviral therapy (ART) in adults with virologically suppressed HIV-1 infections.

“The study was partnered by a study called FLAIR,” which was a similar design in patients who were just starting antiretroviral therapy,” Susan Swindells, MBBS, an investigator on the study, told Contagion®. “They had very similar results: [There were] high levels of suppressions in both arms, patients liked [having the option of] it, and both studies went extremely well.”

ATLAS was a phase 3, open-label, multicenter study that enrolled 616 participants who had HIV-1 RNA <50 copies/mL for ≥6 months without virologic failure on an oral ART regimen of 2 nucleoside reverse transcriptase inhibitors plus 1 integrase strand transfer inhibitor, nonnucleoside reverse transcriptase inhibitors, or a protease inhibitor.

At the point of enrollment, the participants were randomized 1:1 to continue current ART or switch to the treatment arm.

The 308 patients in the treatment arm received oral cabotegravir 30 mg plus rilpivirine 25 mg once daily for 4 weeks for safety monitoring. The participants went on to receive single 3-mL loading doses of cabotegravir long acting (LA) 600 mg (200 mg/mL) and rilpivirine LA 900 mg (300 mg/mL) via intramuscular injection, followed by 2-mL intramuscular injections every 4 ± 1 weeks of cabotegravir LA 400 mg and rilpivirine LA 600 mg.

At week 48, 5 participants (1.6%) in the cabotegravir/rilpivirine arm and 3 (1.0%) in the control arm had HIV-1 RNA >50 copies/mL, meeting the primary end point of noninferiority using the US Food and Drug Administration’s snapshot algorithm.

The investigators also reported that the cabotegravir/rilpivirine arm was noninferior to the current ART arm for the key secondary end point of HIV-1 RNA <50 copies/mL (93% vs 95%, respectively).

A total of 275 participants in the cabotegravir/rilpivirine arm completed an HIV Treatment Satisfaction Questionnaire at week 48, with 98% reporting more satisfaction with the long-acting injectable compared with their daily oral treatment at study entry.


The London Patient: Second Person Ever Reported to Achieve HIV Remission

BY MICHAELA FLEMING

The absence of viral HIV rebound was observed for 16 months following interruption to antiretroviral therapy at 17 months after a single allogenic CCR5 Δ32 hematopoietic stem cell transplant (HSCT) using a no-irradiation approach with only mild graft-versus-host disease.

“It’s far too early to say cure,” Laura Waters, MD, FRCP, a consultant physician at Mortimer Market Centre Sexual Health Clinic in London who is a member of the team of doctors treating the patient, told Contagion®. “This is a case of long-term remission.”

This documentation is similar to only that of the so-called Berlin patient.

The Berlin patient was “cured of HIV” following 2 consecutive HSCTs with total body irradiation. However, it is unclear which aspects of treatment contributed to this only known case of HIV cure.

The London patient has been described as an HIV-infected man with Hodgkin lymphoma who underwent allogeneic HSCT using a homozygous CCR5 Δ32 donor. The nadir CD4 cell count was 290/mm, and the baseline viral load was 180,000 copies/mL.

Antiretroviral therapy (ART) comprising tenofovir disoproxil fumarate/emtricitabine/efavirenz was started in 2012, and during episodes of ART interruption, the investigators observed viral rebound and nucleoside reverse transcriptase inhibitor resistance. The Hodgkin lymphoma was resistant to first-line chemotherapy and other treatment regimens. An unrelated CCR5 Δ32 homozygous donor was identified with 1 allelic mismatch at the HLA-B gene.

Therefore, conditioning was implemented with lomustine, cyclophosphamide, Ara C, and etoposide, which was followed by 3.6 million CD34-positive cells per kg. Graft-versus-host disease prophylaxis consisted of cyclosporine and methotrexate, and in vivo T-cell depletion employed anti-CD52.

The patient developed mild gut graft-versus-host disease; however, full donor chimerism was maintained in the blood. Additionally, ART of rilpivirine, lamivudine, and dolutegravir was continued throughout. Six months following the transplant, complete remission was observed, according to the investigators.

The ART regimen was halted 17 months after HSCT, and plasma HIV viral loads were reported to have remained undetectable (<1.4 copies/mL) at 33 months, with ART drugs not detectable in plasma by liquid chromatography mass spectrometry.

The investigators wrote that at 33 months, “the total HIV DNA in CD4+ T cells showed 2 positive droplets in 1 out of 8 replicated (droplet digital polymerase chain reaction HIV LTR [long terminal repeat], 10^6 cells tested) and no signal in quantitative polymerase chain reaction (<0.69 HIV-gag and <0.65 HIV-LRT copies/million cells).” The team also indicated that “at 16 months post-transplant an HIV-specific Western blot was positive while p24/31 bands were absent.”

VITROS analysis revealed low quantity and quality of HIV antibody titers, and at 3 distinct time points, postransplant quantitative viral outgrowth assay demonstrated no reactivatable virus using 23 million resting CD4-positive T cells. Additionally, postransplant CD4-positive T cells did not express CCR5 and were susceptible in vitro to X4 but not R5 tropic virus.

The investigators concluded that “to our knowledge, this is the longest adult HIV remission observed since the Berlin patient.”

The study, “Sustained HIV-1 Remission Following Homozygous CCR5 Delta32 Allogeneic HSCT,” was presented March 5, 2019, at the Annual Conference on Retroviruses and Opportunistic Infections 2019 in Seattle, Washington. ▲
Ending the HIV Epidemic in the United States: Why Now Is the Right Time

BY ALEXANDRA WARD, MA

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, has been fighting to eradicate HIV/AIDS since the 1980s, when the virus was first discovered.

Now, thanks to a joint effort by multiple arms of the US Department of Health & Human Services (HHS), he is one step closer.

Highlighted in President Donald J. Trump’s State of the Union address earlier this year, the plan to end the HIV epidemic in the United States is in effect, with the goal of achieving a 75% reduction in new HIV infections over the next 5 years and a 90% reduction over the next 10 years.

With 1.1 million people living with HIV, 14% of whom are unaware of their infections, and 38,000 new infections each year, it is clear that HIV is still a problem across the United States. But unlike previous efforts to tamp down new infections, the new plan features simultaneous cooperation from the National Institutes of Health, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the Indian Health Service, among other agencies.

“We don’t have any excuses anymore, since we have the tools...this is the right people in the right place at the right time,” Fauci told the audience at the opening session of the annual Conference on Retroviruses and Opportunistic Infections 2019 on March 4, 2019, in Seattle, Washington. “[It] is the first time an accelerated effort to implement treatment and prevention in the United States has been simultaneously undertaken by multiple HHS agencies that are focusing on highly specific and concentrated target populations.”

Investigators now have the science and the tools to quash the rate of new HIV infections in the United States; they just have to tackle the implementation gap, Fauci said.

Investigators have known for decades that HIV disproportionately affects certain demographics. But the impact of geographic hot spots has begun to come into focus only over the past few years. For example, there are 3007 counties in the United States, but more than 50% of new HIV infections in 2016-2017 were diagnosed in 48 of the counties, as well as Washington, DC, and Puerto Rico, Fauci said. If public health officials can learn how to clear that hurdle, the road to reduction will be a lot easier. The effort will involve a combination of early diagnosis, quick treatment, capitalization on pre-exposure prophylaxis for at-risk individuals, and detection and rapid response to clusters, Fauci said.

“The plan is not a basic or clinical research plan. It’s fundamentally an implementation plan,” Fauci noted. “We really now do not have any excuses to do what the right thing is. We have the tools, [and] many people [here] have been working for decades to create those tools. Right now...this is a moral obligation.” ▲

References are available at ContagionLive.com.
Intra-abdominal Infection With *Eikenella corrodens* in a Woman With Ovarian Cancer

“A bite bug in the belly.”

BY SHARA EPSTEIN, MD; MICHAEL KLEINBERG, MD, PHD; AND JACQUELINE T. BORK, MD

### HISTORY OF PRESENT ILLNESS:

A 63-year-old woman with stage IIIIC ovarian cancer presented to clinic with confusion and hallucinations. A routine blood draw revealed severe anemia, and the patient was admitted for transfusion and observation.

Nine months earlier, the patient had an upper-abdominal hernia repair performed, complicated by a surgical wound infection with poor wound healing. She had several months of negative pressure wound therapy and underwent surgical debridement. Subsequently, she had a skin graft placed, with good wound healing. Two months after the skin graft was placed, the patient reported new abdominal pain, for which a computed tomography (CT) of the abdomen and pelvis was conducted, revealing a complex 7-cm adnexal mass. While awaiting surgery, the patient presented with worsening abdominal pain and distension. A repeat CT of the abdomen and pelvis revealed peritoneal nodules and ascites in addition to the adnexal mass. Paracentesis revealed malignant cells, and a biopsy of the adnexal mass was consistent with serous carcinoma of ovarian origin. The patient received her first round of carboplatin and paclitaxel shortly before presenting with her current complaint of altered mental status and anemia.
CASE STUDY

On the patient’s admission, her vital signs were stable and she was afebrile. A physical exam was significant for a distended abdomen and multiple well-healed scars. Her dentition was good but notable for implants.

STUDIES:
Laboratory values revealed a white blood cell count (WBC) of 1.8 × 10^9/μL (normal, 4.5-11.0) and a hemoglobin of 5.5 g/dL (normal, 11.9-15.7). All other laboratory values were within normal limits. A CT of the abdomen and pelvis was revealing of interval organization of a large amount of free fluid throughout the peritoneal cavity with an enhancing wall (FIGURE 1A). The largest component of this collection measured 30 × 16 cm.

DIAGNOSTIC PROCEDURES AND RESULTS:
A paracentesis was performed. Eight hundred milliliters of serosanguinous fluid was drained. Cell count revealed a WBC of 8100/μL with 81% polymorphonuclear leukocytes and Gram stain with gram-negative rods. Two days later, the culture grew small, gray colonies that pitted the agar, smelled like bleach, and were oxidase negative. The organism was identified as *Eikenella corrodens*. Kirby-Bauer disk diffusion tests demonstrated absent zone of clearance for clindamycin or metronidazole and a large zone for penicillins, fluoroquinolones, and cephalosporins.

TREATMENT:
The patient was treated with ampicillin/sublactam 3 g every 6 hours for possible coinfection with anaerobic organism, with subsequent improvement in symptoms. Interval CT of the abdomen and pelvis revealed an organizing abscess with subsequent gas formation (FIGURE 1B), which was drained, and the culture grew both *E. corrodens* as well as *Bacteroides* species. A transthoracic echocardiogram was revealing of moderate mitral regurgitation, but a subsequent transesophageal echocardiogram was negative for valvar vegetations.

DISCUSSION:
*Eikenella corrodens* is an organism commonly found in the mouth and upper respiratory tract, most often causing periodontitis, as well as skin and soft tissue infections in intravenous drug users who lick their needles before injecting.\(^1\) It has also been described in human bite wound infections.\(^2\) Traditionally *E. corrodens* is described as one of the HACEK organisms, which cause culture-negative endocarditis.\(^3\) Our case describes an unusual instance of a woman with ovarian cancer complicated by an intra-abdominal infection with *E. corrodens*.

There are few case reports and series of intra-abdominal infections with *Eikenella* (TABLE). Sheng et al\(^4\) found 6 cases of intra-abdominal *Eikenella*, 4 of which were liver abscesses, out of a total of 43 cases. None of these cases were associated with ovarian cancer; however, associations were made with various other cancers, including oropharyngeal, lung, breast, neuroblastoma, and colon.

In terms of treatment, *Eikenella* is sensitive to most β-lactam agents. There are no standardized clinical laboratory standards or institute guidelines for interpretation of Kirby-Bauer disk diffusion for *E. corrodens*; however, it has been found in vitro to be resistant to clindamycin and metronidazole.\(^11\) ▲

References available at ContagionLive.com.

### TABLE. Case Reports of Intra-abdominal *Eikenella* Infections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case(s)</th>
<th>Organisms</th>
<th>Treatment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Sheng et al(^6)</td>
<td>4 patients with liver abscesses, 1 intra-abdominal abscess, 1 gallbladder empyema</td>
<td><em>Streptococcus constellatus, Bacteroides fragilis, Streptococcus intermedius</em>, viridans streptococci</td>
<td>Amoxicillin/clavulanate, penicillin G, cephalothin, cefuroxime, cefoxitin, cefotaxime</td>
<td>All patients recovered.</td>
</tr>
<tr>
<td>Jacqua et al(^7)</td>
<td>Liver abscess</td>
<td>Actinomyces</td>
<td>Piperacillin/tazobactam and levofloxacin, then amoxicillin/clavulanate</td>
<td>Recovered</td>
</tr>
<tr>
<td>Chang et al(^9)</td>
<td>Liver abscess</td>
<td><em>Bacteroides fragilis, Streptococcus constellatus</em></td>
<td>Amoxicillin/ clavulanate</td>
<td>Recovered</td>
</tr>
<tr>
<td>Pérez-Pomata et al(^10)</td>
<td>Splenic abscess</td>
<td><em>Eikenella</em> only</td>
<td>Cefotaxime</td>
<td>Recovered</td>
</tr>
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</table>

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References available at ContagionLive.com.
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