The morbidity and mortality associated with the opioid epidemic are substantial and increasing in the United States. Over the past 2 decades, heroin use and heroin-related overdoses have increased dramatically. Heroin use increased 65% between 2002 and 2013, and drug overdoses accounted for 70,237 deaths in 2017, with 68% of those involving an opioid.

The US overdose epidemic is associated with 2 distinct but interconnected trends: a 15-year increase in fatal overdoses due to prescription opioids and a recent surge in fatal overdoses due to illicit opioids such as heroin and fentanyl. Rapidly rising increases in heroin use are paralleled by increases in injection drug use, thus increasing exposure to blood-borne infections such as viral hepatitis, HIV, and serious bacterial infections.

The estimated per-act probability of acquiring HIV from an infected source via needle sharing during injection drug use is 63 per 10,000 exposures compared with 138 per 10,000 exposures for condomless receptive anal intercourse. The increasing morbidity and mortality from opioid and other substance use disorders is a call to action for ID providers.
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 per 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 dofetilide 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. However, the occurrence of autoimmune disorders has been rare in HIV-1 infected patients treated with BIKTARVY. Patients with a history of autoimmune disorders may be at increased risk for these events. Monitor patients for signs and symptoms of immune reconstitution syndrome.

- 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.
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.**

3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor.

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.

DOSEAGE AND ADMINISTRATION
Also see Drug Interactions 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:
• dolutegravir due to the potential for increased dolutegravir 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: Co-administration 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 products 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, 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 products who have renal impairment and/or are taking nephrotoxic agents including NSAIDs 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-naive 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 attempts, and depression 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%), Creatine Kinase ≥10.0 x ULN (4%, 4%), Neutrophil % <25% (2%, 3%), and Increased 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.
In Virologically Suppressed Adults: The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on 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.

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.
- 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: During pregnancy to inform a drug-associated risk of 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 breastfeeding 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 all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. FTC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is unknown if TAF is present in animal milk. Because of the potential for HIV transmission in human-negative infants, developing viral resistance in HIV-positive infants, and adverse reactions in nursing infants, mothers should be instructed not to breastfeed.

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.

OVERDOSAGE:

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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With the Opioid Epidemic, Communities See Dramatic Increases in Infectious Diseases

Rising incidence of viral and bacterial infections has accompanied the opioid crisis, but it also presents new opportunities for multidisciplinary treatment and preventive care.

BY HERMIONE HURLEY, MD, MBCHB; ALIA AL-TAYYIB, PHD, MSPH; AND SARAH E. ROWAN, MD
ANTIBIOTIC RESISTANCE: PATIENTS DON’T GET IT, AND WE NEED TO HELP

Nothing caught my eye on Twitter the other day. Someone had tweeted a study whose results showed that 72% of respondents to a survey in South Africa believed that antibiotic resistance is due to the human body’s increasing resistance to antibiotics, not the bacteria that actually cause infections—a shocking number, so I did some digging around to see whether it was an outlier. Was it? Not even close. The World Health Organization performed a study across 12 countries to examine public perceptions on antibiotic resistance and found that 76% of respondents thought the same thing. Although differences among countries were noted, more than half of those surveyed held this belief. Results from some studies have shown this conviction is even more common. The belief that antibiotics can treat viral infections is also persistently shown at >50% across studies.

This is not good news. However, does it really seem surprising? Without an understanding of microbiology, why would we expect patients to understand what antibiotics actually do and how bacteria evolve to be resistant to them? The observation that a course of azithromycin that seemed to work previously but failed a second time does seem like the body has become resistant to the effects of the drug. It also parallels patient experiences with other medications. After all, how much education about medical microbiology do most people receive in school?

Beyond these easily disproved notions, we shoulder a lot of blame for people misunderstanding antibiotic resistance. When I think of the many times that I have heard clinicians say that they are giving a patient a “powerful antibiotic” with the intention of bolstering patient confidence in the choice, it leaves me wondering what a patient has learned from the experience. How about when people say that a patient has a particular “bug” being treated?病人 have been shown to decrease antibiotic use and symptoms and escalating care when necessary have been shown to decrease antibiotic use for these infections and that contain directions for treating patients, this fear may be overblown. Ambulatory “toolkits” for respiratory viral infections that explain basic microbiology and antibiotic resistance are psychological. Although practitioners often report in surveys that they feel compelled to prescribe antibiotics to satisfy patients, this fear may be overblown. Ambulatory “toolkits” for respiratory viral infections that explain basic microbiology and the futility of antibiotic use for these infections and that contain directions for treating symptoms and escalating care when necessary have been shown to decrease antibiotic use with high degrees of patient satisfaction. Explaining antibiotic resistance itself may be difficult, but even brief descriptions of what it is can help. We should adjust our language, as well, because terms that are convenient for us can be misleading. Something as simple as replacing the use of misuse of any material or information presented in this publication are those of the authors and do not necessarily reflect the opinion or policy of Contagion®.

Addressing these misconceptions is important. Many of the pressures that lead to increasing antibiotic resistance are psychological. Although practitioners often report in surveys that they feel compelled to prescribe antibiotics to satisfy patients, this fear may be overblown. Ambulatory “toolkits” for respiratory viral infections that explain basic microbiology and the futility of antibiotic use for these infections and that contain directions for treating symptoms and escalating care when necessary have been shown to decrease antibiotic use with high degrees of patient satisfaction. Explaining antibiotic resistance itself may be difficult, but even brief descriptions of what it is can help. We should adjust our language, as well, because terms that are convenient for us can be misleading. Something as simple as replacing the use of misuse of any material or information presented in this publication are those of the authors and do not necessarily reflect the opinion or policy of Contagion®.

Our feature article this month—by Hermione Hurley, MD, MBChB; Alia Al-Tayyib, PhD, MSPH; and Sarah E. Rowan, MD—explores the dramatic increases in infectious diseases in the wake of the opioid epidemic.

As always, enjoy this issue, and keep up with us at ContagionLive.com.
Same-Day PrEP Initiation: Simplifying Access and Dismantling Barriers to Care

BY ANIRUDDHA (ANU) HAZRA, MD

The US Centers for Disease Control and Prevention (CDC) estimated that as of 2015, approximately 1.2 million individuals were eligible to take pre-exposure prophylaxis (PrEP) to prevent HIV.1 However, a 2017 study found that only approximately 100,000 individuals were actually taking PrEP in the United States.2 Several groups have addressed the challenge of increasing PrEP uptake as health care professionals consider novel strategies to deliver this resource to populations in need.

Traditionally, municipal and community-operated sexually transmitted disease (STD) clinics have been at the forefront of tackling challenges related to sexual and gender minority health. Unsurprisingly, STD clinics have reported increased patient interest in PrEP and have also observed an uptick in PrEP use and adherence.3 However, these clinics often face challenges in providing longitudinal patient care because of limited resources and capacity. As a result, STD clinics frequently become venues for PrEP referral rather than initiation, a model that only adds another obstacle to the PrEP engagement cascade.

Kamis and colleagues conducted a single-site study in Denver, Colorado, to examine whether same-day PrEP initiation at a busy, urban STD clinic would be feasible and safe and lead patients to continue PrEP care.4 Eligible participants had to be at least 18 years of age and meet the indications for PrEP (PrEP to prevent HIV).1 However, a 2017 study found that only approximately 100,000 individuals were actually taking PrEP in the United States.2

Participants were excluded if they had HIV or a recent bacterial STI (STI) or signs and symptoms of acute HIV infection. The patients were scheduled for 1-month follow-up visits at participating clinics based on patient preference and insurance status. Additionally, the patient navigator contacted the participants 1 week after enrollment to assess any adverse effects of medication. The navigator administered a satisfaction survey to all participants 3 months after enrollment, and reviewed the medical records of each participant up to 6 months after enrollment.

The investigators reviewed pregnancy and rapid HIV results during the clinic visit; any other abnormal laboratory results were communicated to patients within 2 days of enrollment. Participants were required to meet with a patient navigator, who confirmed readiness to initiate PrEP and conducted a financial screening, assessing income and insurance status. The patients were scheduled for 1-month follow-up visits at participating clinics based on patient preference and insurance status.

Of the 100 participants enrolled, the median age was 28 years; the overwhelming majority (98%) were cisgender males, all of whom were men who have sex with men (MSM); and nearly half of study participants (48%) identified as non-Hispanic white. Of note, no participants had any abnormal baseline laboratory results. Seventy-eight percent of participants attended at least 1 follow-up visit with a PrEP provider, and more than half (57%) attended at least 2 follow-up visits within 180 days of enrollment. No HIV seroconversions were observed by chart review within the 6-month follow-up period. In multivariable analysis, after adjusting for age, race/ethnicity, income, and insurance status, only income was associated with follow-up appointment attendance, revealing that each $10,000 increase in income was associated with a 1.7-fold increase in the odds of attending a PrEP follow-up appointment. Fifty-four participants responded to the satisfaction survey at 3 months and reported satisfaction with the option for same-day PrEP initiation; 96% of respondents reported plans to continue using PrEP.

Simplifying medication access has been proved effective in engaging patients in care and promoting adherence. Same-day antiretroviral (ART) initiation has repeatedly been associated with improved ART uptake, retention in care, and virologic suppression.5 This study demonstrates that same-day PrEP initiation is indeed feasible. For the 100 study participants, this model was safe; however, given the limited sample size, generalizing these data is difficult. Finally, the percentage of participants retained in PrEP care at 6 months through this model mirrors national trends.6 Unsurprisingly, lower income is negatively associated with PrEP retention, underscoring the systemic barriers patients face to accessing not only sexual health care but general health care as well.

As the United States continues to scale up PrEP initiation and promote adherence, following the official grade A recommendation from the US Preventive Services Task Force, uptake in areas with limited resources is vital.10 The CDC reported that from 2014 to 2017, PrEP use among MSM in urban areas increased from 6% to 35%; however, this trend is blunted in the African American and Hispanic/Latinx populations, low-income individuals, and those who are uninsured.11 Implementation of a same-day PrEP initiation model is only 1 part of the solution. Inclusion of insurance enrollment, mental health, employment, and housing services is critical in engaging and retaining patients taking PrEP to help end the HIV epidemic.

References are available at ContagionLive.com.

HIGHLIGHTED STUDY

Same Day PrEP Initiation During Drop-In Sexually Transmitted Diseases Clinic Appointments


TABLE. CDC Criteria for PrEP Use6

<table>
<thead>
<tr>
<th>TARGET POPULATION</th>
<th>MEN WHO HAVE SEX WITH MEN</th>
<th>HETEROSEXUAL MEN AND WOMEN</th>
<th>PEOPLE WHO INJECT DRUGS</th>
</tr>
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<tbody>
<tr>
<td>Substantial risk factors for acquiring HIV infection (if at least 1 is present, PrEP should be considered)</td>
<td>• Sexual partner with HIV</td>
<td>• Sexual partner with HIV</td>
<td>• HIV-positive injection partner</td>
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<td>• Recent bacterial STI</td>
<td>• Recent bacterial STI</td>
<td>• Sharing of injection equipment</td>
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<td></td>
<td>• Inconsistent condom use</td>
<td>• Inconsistent condom use</td>
<td>• Recent drug treatment (but currently injecting)</td>
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<td></td>
<td>• Commercial sex work</td>
<td>• Commercial sex work</td>
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<tr>
<td>Clinical eligibility</td>
<td>• Documented negative HIV test before PrEP prescription</td>
<td>• No signs/symptoms of acute HIV infection</td>
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<tr>
<td></td>
<td></td>
<td>• Normal renal function</td>
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</tbody>
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CDC indicates US Centers for Disease Control and Prevention; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection. Adapted from CDC’s Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017 Update.6

IN THE LITERATURE


IN THE LITERATURE

Table showing the CDC criteria for PrEP use.
Where to Treat Uncomplicated HCV? Assessing the Impact of Shifting Care From Specialists to PCPs

BY SEAN BULLIS, MD; AND ANDREW J. HALE, MD

Hepatitis C virus (HCV) infection remains a common cause of chronic liver disease worldwide, with a global prevalence of 1%. Despite the advent of highly effective antiviral regimens, the health burden of HCV remains substantial, with approximately 20,000 attributable deaths annually in the United States alone. The World Health Organization has thus proposed an HCV containment target of an 80% decrease in incidence by 2030. However, this lofty goal is at odds with the current epidemiology of HCV; in the United States, HCV incidence has steadily increased over the past decade, which is largely attributable to the current opioid epidemic among people who inject drugs (PWID).

Previous treatment regimens that included pegylated interferon were minimally efficacious and challenging for patients to tolerate. With the advent of direct-acting antivirals (DAAs), treatment has become more tolerable and cure rates have increased markedly. Strikingly, though, less than 40% of individuals with known infection undergo antiviral therapy, with current systems of disease management hampered by (a) limitations in expertise among primary care professionals (PCPs) in the treatment of hepatitis C and (b) barriers to HCV specialty access. A critical need exists to overcome these obstacles, and without change, the prevalence of HCV will progressively increase, exacerbating the global negative impact of this disease.

One promising proposal to greatly increase access to DAA HCV therapy is to keep this treatment with appropriately trained PCPs, in contrast with referring patients to infectious disease, gastroenterology, or hepatology subspecialists. An important question in this transition, however, is whether PCPs can maintain the high rates of sustained virologic response (SVR) seen in subspecialty HCV care, in which cure rates are typically >95% for patients completing therapy. This question is particularly pertinent among PWID, who represent a high percentage of patients with new infections and present unique challenges in accessing HCV therapy.

In a retrospective study, Wade et al provided important insight into this dilemma. In their trial, the authors randomized PWID with chronic HCV to receive DAAs in primary care (PC) or hospital specialist outpatient clinic (SOC) settings. The trial took place at 13 PC sites staffed by general practitioners who provided opioid substitution therapy in Australia and New Zealand between 2015 and 2018. The purpose of the study was to determine whether treatment in the PC setting was noninferior to standard of care regarding SVR. The investigators also examined comparison of treatment initiation, rates of SVR at week 12 (SVR12), and the care cascade (defined as diagnosis using HCV antibody and transient elastography, assessment, treatment initiation, and cure) by study arm. The study excluded patients with cirrhosis, HCV treatment experience (with the exception of pegylated interferon/ribavirin), and HIV or hepatitis B virus coinfection.

Overall, 144 participants with genotype 1 or 3 chronic HCV infection were recruited and 136 were randomized; nearly all were PWID, and the majority were on opioid substitution therapy. For patients with genotype 1, the antiviral regimen was 12 weeks of paritaprevir/ritonavir/ombitasvir/dasabuvir; for patients with genotype 1a, the investigators added weight-based ribavirin. For patients with genotype 3, the authors used 12 weeks of sofosbuvir and daclatasvir.

In the per-protocol analysis, 100% of patients who completed therapy in PC (n = 28) achieved SVR12, which was noninferior to the SOC arm. Significant dropout was observed in both arms during the trial. However, intention-to-treat analysis revealed that a statistically significant higher percentage of patients initiated treatment in the PC setting compared with those receiving SOC (75% vs 34%, P < .001). Of patients who did initiate therapy, only 13% failed to complete liver assessments or were lost to follow-up in the PC arm compared with 36% of patients in the SOC arm. Among all participants in the intention-to-treat analysis, including patients who never started therapy or dropped out of treatment, SVR12 in the PC setting was significantly higher compared with SOC (49% vs 30%, P = .043). Thus, in sum, the cascade of HCV care was, at a minimum, noninferior in the PC arm.

This is one of the first randomized, controlled trials to examine the initiation of DAA treatment and HCV outcomes in a PC versus specialist clinic setting among PWID. The authors concluded that community-based treatment of uncomplicated hepatitis C improved treatment uptake and cure. Although this was a noninferiority trial, the PC arm care cascade appeared superior, with a higher percentage of patients overall achieving SVR12. Despite these findings, access to initiation of HCV treatment in nonspecialist settings remains low. HCV specialty clinics may be better for treating predominantly complicated chronic HCV infection—HIV or hepatitis B coinfection, cirrhosis, infection in treatment-experienced patients, or other complicating factors—whereas uncomplicated HCV should perhaps increasingly become the domain of PCPs. Broadening access to community-based practices and easing restrictions on prescriber type may have vast implications for effective treatment and cure of HCV.

References are available at ContagionLive.com.
Combination Therapy for MRSA Bloodstream Infections: Still a Question Mark
By Alexandra Ward, MA

The question of combination therapy versus monotherapy for methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections is a widely debated one. Now the results of a new study by a team of investigators from Wayne State University and the University of California at San Francisco show that a daptomycin/β lactam combination is a potential treatment option for serious MRSA infections, yet further research is needed. The study, which was conducted at 2 academic medical centers between 2008 and 2018, was published in *Clinical Infectious Diseases*.

“Combination of vancomycin or daptomycin with a β-lactam has been shown in vitro to be synergistic and has the potential to decrease the emergence of resistance in *S aureus*,” Michael J. Rybak, PharmD, PhD, MPH, professor of pharmacy and medicine and director of the Anti-Infective Research Laboratory at the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University and a coauthor on the study, told Contagion® regarding the motivation behind the research.

“Most clinical studies to date have shown a benefit in shortening the days of bacteremia. However, there is limited evidence thus far that combination therapy has improved outcomes such as mortality and recurrence of infection,” Rybak said.

The trial included 229 participants with MRSA bloodstream infections who were treated with daptomycin >72 hours and for whom treatment was initiated within 5 days of culture collection. Participants in the daptomycin/β-lactam (DAP + BL) group received a β-lactam for ≥24 hours, initiated within 24 hours of their receiving daptomycin.

The primary outcome in the study was composite clinical failure (60-day all-cause mortality and/or 60-day recurrence), and the analysis was adjusted for confounding using inverse probability of treatment weighting.

A total of 72 participants were included in the DAP + BL group compared with 157 participants in the daptomycin group. The combination arm was associated with improved clinical outcomes (odds ratio [OR], 0.362; 95% CI, 0.164, 0.801; adjusted OR, 0.386; 95% CI, 0.175, 0.853).

“DAP plus β-lactam therapy was associated with reduced composite definition for clinical failure, mortality, and recurrence of infection. There was no difference in days of bacteremia,” Rybak, a member of the Contagion® Editorial Advisory Board, explained. “There was a higher rate of nephrotoxicity in the combination compared with the monotherapy group (10.8% vs 2.9%; P = .046), and rates of *Clostridioides difficile*-associated diarrhea were higher versus the monotherapy group but not statistically significant (1.3% vs 5.6%).”

The team was surprised that the days of bacteremia were not shorter in the combination therapy arm.

“While the combination of daptomycin plus a β-lactam looks promising as a treatment option for serious MRSA infections, further research in well-controlled clinical trials is needed,” Rybak concluded.

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**CDC Warns of Link Between Overseas Hospitalization, CPOs, and *C auris***
By Jared Kaltwasser

A new report from the US Centers for Disease Control and Prevention (CDC) notes that overseas hospitalization and carbapenemase-producing organism (CPO) colonization or infection are potential warning signs for the presence of *Candida auris*.

The warning, published in the CDC’s *Morbidity and Mortality Weekly Report*, comes after a case in Maryland in September 2018 in which a patient was admitted to the hospital with multiple CPO colonizations/infections. The patient had previously spent a month in a hospital in Kenya after suffering a cerebral hemorrhage while visiting the country. The patient’s treatment there involved several operations and complications, as well as the insertion of a feeding tube.

After the patient was medically evacuated to the United States, hospital staff tested the patient for *C auris*. The patient was found to have *C auris* colonization but not infection. The hospital then evaluated 21 patients who had been in the same unit, but none of those patients tested positive for *C auris* colonization or infection.

The CDC suggests that anyone who has been hospitalized overnight overseas in the past 12 months be screened for *C auris*. The agency also recommends contact precautions and CPO screening for any patient with an overnight overseas hospital stay in the previous 6 months.

Richard B. Brooks, MD, of the Division of Healthcare Quality Promotion at the CDC’s National Center for Emerging and Zoonotic Infectious Diseases, told Contagion® that overseas travel is a risk factor for *C auris*, but awareness of the link between *C auris* and receiving care overseas varies.

“It’s important to get an accurate and complete travel history when admitting a patient to the hospital, but it’s not always done,” Brooks said. “During the Ebola outbreak in West Africa in 2015 and the Zika outbreak in 2016, providers became much more focused on getting this information. But as those outbreaks resolved, the attention paid to collecting this information also waned.”

In their report, Brooks and colleagues urged providers and hospitals to be on the lookout for *C auris* in travelers hospitalized overseas even if their destination country is not associated with known problems with *C auris*.

In patients indicated for *C auris* screening, Brooks cautioned, most routine hospital testing platforms can easily misidentify *C auris*, and he noted that commercial testing is not currently available to hospitals. However, he said the CDC’s Antibiotic Resistance Laboratory Network will perform the test for free. Health care facilities can request testing through their state health departments.
Preclinical Trial of TDF Vaginal Ring for PrEP Ends Early
By Jonna Lorenz

A preclinical trial of a tenofovir disoproxil fumarate (TDF) intravaginal ring for HIV pre-exposure prophylaxis (PrEP) ended early after 8 of 12 women unexpectedly developed vaginal ulcers.

The National Institutes of Health-funded study, published in The Lancet, included 17 sexually active women, 12 of whom received intravaginal rings with TDF. None of the 5 women in the placebo group experienced vaginal ulcers.

“The mechanisms by which the drug ring, and not the placebo ring, led to this unanticipated finding are not yet fully understood,” corresponding author Betsy Herold, MD, director of the Translational Prevention Research Center at Albert Einstein College of Medicine, told Contagion. “We did observe increases in inflammatory markers in women using the TDF compared [with] placebo ring by examining, for example, gene expression in biopsy tissue. The findings suggest that sustained levels of intracellular tenofovir-diphosphate, the active form of the drug in cells, and/or other metabolites released by the TDF but not placebo ring induce inflammation and may disrupt epithelial repair, which, in the setting of microabrasions associated with ring use and/or sex, may predispose to ulceration.”

All ulcers resolved after the rings were removed. Only 2 participants in the TDF group completed the 3-month study with continuous ring use and monthly ring changes. Investigators detected ulcers an average of 32 days after TDF ring use began, with 8 participants discontinued use early as a result. Rings were electively removed from the other 2 participants in the TDF group at 20 and 23 days.

Women in the TDF group had a 5- to 15-fold increase in cytokines or chemokines detected in the cervicovaginal fluid samples. Although the reason for the unexpected results is unknown, differences between this study and earlier studies include the patient population and the duration of the study.

“[Although] the results of this particular ring study were disappointing, it is important to emphasize that lessons learned will help us in developing other products,” Herold said. “For example, the results highlight the need to readjust the current preclinical models of safety, which did not predict the outcome of this trial. There is an unmet need for safe and effective PrEP for women that addresses some of the challenges with adherence, and rings have the potential to meet that need. Thus, more research is needed.”

Opioid Injection in Rural US Communities Challenges Efforts to End the HIV Epidemic
By Michaela Fleming

In February's State of the Union address, President Donald Trump announced his plan to end the HIV epidemic in the United States. The plan seeks to decrease the number of new HIV infections in the United States by 75% in 5 years and 90% in 10 years and end the epidemic completely by 2030.

In a new viewpoint published in JAMA, Andrea M. Lerner, MD, and Anthony S. Fauci, MD, both of the National Institute of Allergy and Infectious Diseases, addressed how injection opioid use in rural US communities is a growing threat to the goal of ending the HIV epidemic.

The rise of opioid injection use in these communities has increased the HIV risk in populations that are both demographically and geographically distinct from previously identified high-risk groups. This creates a complex situation, as these communities do not have the infrastructure or the resources to control the situation.

Fauci and Lerner presented the example of an HIV outbreak detected in Scott County, Indiana, in November 2014, driven by the widespread injecting of an extended-release formulation of oxymorphone among the community. Through epidemiologic analysis and viral molecular sequencing, health investigators determined that the HIV transmission in the county likely began in 2011, with accelerated growth occurring in 2014. This suggests that most of the infections transmitted during this outbreak had already occurred by the time a public health emergency was declared in 2015.

Following this outbreak, the US Centers for Disease Control and Prevention (CDC) developed a vulnerability score to identify counties at high risk for HIV transmission. The CDC identified 220 counties across 26 states, which were reported as “overwhelmingly rural.” Of concern, less than a quarter of the vulnerable counties were operating needle and syringe exchange programs, which have proved effective elsewhere.

“This lack of harm-reduction services threatens to reverse decades of progress and recapitulate the devastating effects that IDU [injection drug use]-related HIV transmission had during earlier years of the HIV epidemic in the [United States],” Fauci and Lerner wrote.

Despite the barriers to adherence to prevention and treatment methods, the authors indicated that using a proactive strategy is fundamental to reducing the HIV transmission. Per the authors, it is also critical to offer sexual health services including HIV testing, counseling, and linkage to care to improve early detection of HIV transmission and prevent further outbreaks.

Failure to correct the misperception that HIV cannot affect previously uninvolved communities, along with neglecting to implement HIV prevention and treatment tools, will in turn increase the risk of a rebound in the incidence of IDU-related HIV cases, representing an obstacle to ending the HIV epidemic in the United States.
The Clinical and Laboratory Standards Institute (CLSI) Subcommittee on Antimicrobial Susceptibility Testing (AST) held its 2019 meetings in January and June, introducing several new and revised breakpoints. Although the subcommittee approved certain breakpoints in June 2019, they are subject to change prior to official approval of the meeting minutes at the January 2020 meeting.

**NOTEWORTHY NOVEL AND REVISED BREAKPOINTS**

**Azithromycin for Neisseria gonorrhoeae**

Current recommendations from the US Centers for Disease Control and Prevention and the World Health Organization support combination therapy with ceftriaxone (250 mg, intramuscular) plus azithromycin (1 g, oral) for the treatment of uncomplicated gonorrhea. The hope for dual therapy of agents with different mechanisms of action is to slow the emergence and spread of resistance to ceftriaxone, as resistance of *N gonorrhoeae* to other antimicrobial classes (eg, fluoroquinolones) has been documented in recent years. Azithromycin minimal inhibitory concentration (MIC) distribution data and clinical efficacy data were reviewed at the June 2018 meeting, and a “susceptible-only” breakpoint of ≤1 mg/L was justified by the wild-type susceptibility distribution and lack of sufficient clinical efficacy data for isolates with MICs between 2 and 8 mg/L. This new breakpoint was subsequently published in the 2019 (29th edition) of the M100 document (Table 1). A comment that azithromycin use is required as part of a combination regimen was also included.

**Polymyxins (polymyxin B and colistin)**

New antibiotics are not available in many parts of the world, so polymyxins are often last-resort agents used to treat multidrug-resistant pathogens despite poor clinical outcomes after their use in many studies. Even though newer, more effective antibiotics are available in the United States, recent estimated sales data reveal that colistin use is still significantly higher than that of the newer (ie, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin) and more expensive branded agents.

Previously, the CLSI had polymyxin B breakpoints for *Pseudomonas aeruginosa* but no interpretive criteria for Enterobacteriaceae. The CLSI’s “silence” on Enterobacteriaceae—no current breakpoint and only an epidemiological cutoff value (ECV)—was thought not to be in patients’ best interests because ECVs cannot be used by hospital laboratories nor published as clinical breakpoints. After a review of pharmacokinetic/pharmacodynamic (PK/PD), outcomes and MIC distribution data, the CLSI determined that a breakpoint could not be <2 mg/L, as this would cut into the wild-type distribution of Enterobacteriaceae. Polymyxin B and colistin breakpoints were ultimately set for Enterobacteriaceae, *P aeruginosa*, and *Acinetobacter* spp at ≤2 mg/L (intermediate) and ≥4 mg/L (resistant), with no susceptible category. Rationale for an intermediate-only breakpoint suggests a black box warning that these agents are of limited clinical efficacy even for isolates with MIC values <2 mg/L. The subcommittee also suggested that several warnings/comments be added to polymyxin B/colistin breakpoints.

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**What’s New From the CLSI Subcommittee on Antimicrobial Susceptibility Testing**

Updates include novel and revised breakpoints for azithromycin, polymyxins, daptomycin, and cefiderocol.

**BY MÉLANIE T. MAHONEY, MPH, PHARMD STUDENT, AND ELIZABETH B. HIRSCH, PHARMD, RPH**

Mahoney is a fourth-year pharmacy student at the University of Minnesota in Minneapolis.

Hirsch is an assistant professor at the University of Minnesota College of Pharmacy. Her translational research program is focused on the detection and treatment of resistant bacterial infections. She is an appointed adviser to the CLSI Subcommittee on AST.
maltophilia. 

resistant Enterobacteriaceae, gram-negative bacteria, including carbapenem-demonstrated in vitro activity against Cefiderocol disk diffusion breakpoints of 6 mg/kg/mL. 

that these breakpoints are based on a regimen separate daptomycin breakpoints were approved to susceptibility among reviewed unpublished microbiological data the AST Subcommittee revisited this issue and the new daptomycin breakpoints for other infectious diseases specialist is recommended. "Enterococcus faecium. 

and is intended for serious infections due to dosage regimen of 8-12 mg/kg/day in adults states, "The SDD category is based on a breakpoints for Enterococcus spp. 

daptomycin breakpoints for Enterococcus spp to include a range of MICs (2-4 mg/L) that would be considered "susceptible-dose dependent" (SDD). The AST Subcommittee made the approval after reviewing several studies that found worse clinical outcomes with daptomycin MICs of 3 to 4 mg/L compared with MICs ≥2 mg/L when treating patients with vancomycin-resistant Enterococcus bacteremia. 

More recently, at the January 2019 meeting, the AST Subcommittee revisited this issue and reviewed unpublished microbiological data from a 3-center study showing a difference in susceptibility among Enterococcus spp. Revised daptomycin breakpoints were approved to separate E faecium and other Enterococcus spp in an effort to more accurately reflect the susceptibility differences between E faecium and other Enterococcus spp. A comment to be included with the breakpoints for E faecium states, "The SDD category is based on a dosage regimen of 8-12 mg/kg/day in adults and is intended for serious infections due to Enterococcus faecium. Consultation with an infectious diseases specialist is recommended." Similarly, the AST Subcommittee approved the new daptomycin breakpoints for other Enterococcus spp (Table 1), with a comment that these breakpoints are based on a regimen of 6 mg/kg/mL.

Cefiderocol disk diffusion breakpoints Cefiderocol is a novel cephalosporin not yet approved by the FDA. This agent has demonstrated in vitro activity against gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, P aeruginosa, Acinetobacter spp, and Stenotrophomonas maltophilia. 

At the June 2018 meeting, the AST Subcommittee approved cefiderocol MIC breakpoints based on microbiological, PK/PD, and clinical data from the sponsor. 

At the January 2019 meeting, the sponsor presented data for MIC/disk correlation studies and proposed disk diffusion breakpoints. These breakpoints for cefiderocol and Enterobacteriaceae, P aeruginosa, Acinetobacter spp, and S maltophilia (Table 2 online) were approved at the January 2019 meeting and confirmed at the June 2019 meeting following review of reproducibility data. It was also proposed that the subcommittee continue to monitor these interpretive criteria as laboratories begin to test the drug.

NOTEWORTHY NONBREAKPOINT NEWS Fosfomycin susceptibility testing Fosfomycin susceptibility testing issues have been a topic of discussion among a fosfomycin ad hoc working group (AHWG). Prompted by a recent publication, the AHWG was originally tasked with making a recommendation on colonies within the zone of inhibition for interpreting disk diffusion testing against Escherichia coli. 

Ultimately, the AHWG recommended leaving the current CLSI recommendation as is, without additional comments about inner colonies, until further data are available. 

In 2019, the AHWG evaluated unpublished data presented by Eric Wenzler, PharmD, BCPS, BCIDP, AAHIVP, and colleagues that questioned whether the current recommendation of addition of glucose 6-phosphate (G6P) for in vitro susceptibility testing is physiologically accurate, as urine appears to be devoid of G6P. 

The Enterobacteriaceae organisms, E coli and Klebsiella pneumoniae, both use nutrient transport uptake systems, the glyc erol 3-phosphate transporter and a hexose phosphate transporter (UhpT), to bring fosfomycin into the bacterial cell. 

Because the UhpT system is induced by its substrate, G6P, in vitro testing with G6P supplementation may not accurately reflect in vivo conditions if the urine is devoid of G6P where the site of action is expected for cystitis. Other recent PK/PD and clinical outcomes data also highlight variability of oral fosfomycin concentrations in the urine and unexpectedly high failure rates in randomized clinical trial settings. 

The data presented by Wenzler evaluated agar dilution MIC testing and urinary bactericidal titers (UBTs) with and without G6P. MICs without G6P were universally higher compared with those supplemented with G6P, whereas UBTs without added G6P were much lower compared with UBT with G6P. After discussion, the subcommittee advised retaining G6P until further data are available and also recommended revisiting broth microdilution testing for fosfomycin.

Colistin testing methods Because of difficulty in polymyxin susceptibility testing novel methods for testing have recently been explored. Data comparing 2 new methods of colistin susceptibility testing, colistin disk broth elution (CBDE) and colistin agar test (CAT), were presented and subsequently approved as provisional methods for both Enterobacteriaceae and P aeruginosa until further data from additional manufacturers can be evaluated. Using the CBDE method, 10-µg colistin disks are incubated at room temperature for 20 minutes in tubes containing prespecified volumes of cation-adjusted Mueller-Hinton broth to achieve varying concentrations of colistin. The bacterial inoculum is then added and vortexed. The broth tubes are incubated for 18 to 20 hours, and the MIC is read based on presence/absence of growth in each tube. In the CAT method, Mueller-Hinton agar plates are prepared with increasing concentrations of colistin (eg, 0.4, 0.5, 1.0, 2.0, 4.0 mg/L). These colistin agar plates are then inoculated with either a 1-µL or 10-µL loopful of a 1:10 dilution of inoculum and incubated for 16 to 20 hours. Plates are then read where any visual growth of organism is read as positive. 

References are available at ContagionLive.com.

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<th>TABLE 1. Notable New and Revised CLSI Interpretive Categories and MIC Breakpoints a,b</th>
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CLSI indicates Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration; N/A, absence of MIC breakpoint.

a Previous breakpoints are cited from the 2018 (28th edition) of the M100 document.

b Approved at the 2019 meetings or published in the 2019 (29th edition) of the M100 document.
Investigational Treatments for *C difficile* Infection

The high recurrence rates of *Clostridioides difficile* infection highlight the need for novel agents with unique mechanisms of action for treating the infection.

**BY RAVINA KULLAR, PHARMD, MPH, FIDSA; MAI-CHI N. TRAN, PHARMD, BCPS; AND ELLIE J. C. GOLDSSTEIN, MD, FIDSA, FSHEA**

(continued from cover page)

as it was inferior to vancomycin for mild and moderate disease, with increased recurrence rates. Meanwhile, fidaxomicin was raised to a first-line option. For second or subsequent recurrences, the guidelines also recommend fecal microbiota transplant (FMT).

Fidaxomicin has demonstrated several meaningful differences compared with currently available CDI treatment options. Animals studies have revealed that fidaxomicin exposure led to minimal microbiota disruption and did not promote colonization by vancomycin-resistant enterococci and *Klebsiella pneumoniae*, whereas exposure to vancomycin did promote colonization by these bacteria. Host microbiome preservation is thought to be the primary driver of fidaxomicin's reduced CDI recurrence rates compared with vancomycin. Albeit recurrence rates are less than vancomycin, they are still at ~20%. Fidaxomicin's high price tag compared with that of vancomycin and conflicting data from studies on its overall cost-effectiveness have resulted in relatively poor clinical uptake. For patients with prior vancomycin failure, fidaxomicin is recommended rather than administering the same failed treatment—primarily to save drug costs all while increasing overall health care costs and decreasing patients' quality of life.

The IDSA treatment guidelines recommend FMT for recurrent CDI. Based on the principle that restoration of a healthy gut microbiota will reduce susceptibility of a patient to CDI, cure rates of >80% have been reported in most clinical trials. FMT can be administered via oral capsules, lower gastrointestinal (GI) tract procedure (colonoscopy, retention enema), or upper GI tract procedure (nasojejunal/nasoduodenal tube). The US Food and Drug Administration (FDA) has not approved FMT but has allowed its use as an investigational drug. Major concerns with FMT are the lack of long-term studies, the risk of transferring infectious pathogens from the donor to the recipient, and the development of immune-mediated diseases such as irritable bowel disease. Additionally, the FDA issued a safety alert in June 2019 after a patient died and another suffered an invasive infection, with both illnesses caused by extended-spectrum β-lactamase–producing *Escherichia coli* post-FMT from the same donor.

We recommend FMT as last resort, with screening of the donor's stool as a prerequisite.

Clearly, the currently approved CDI agents are not optimal. Improved therapeutic alternatives with a significant protective and restorative effect on the intestinal microbiome are needed for CDI treatment to ultimately lead to better efficacy and lower recurrence rates. This article will provide a brief review of select drugs in the pipeline for CDI and discuss lessons learned from prior failed clinical trials.

**NOVEL AGENTS IN LATER-STAGE DEVELOPMENT**

Ribaxamase (SYN-004) offers a unique approach to the prevention of CDI, namely protection of patients' natural microbiome. Preserving the normal microbiome is key to preventing CDI, as disruption of the microbiota is at the core of CDI pathogenesis. Upon microbiome disruption, patients lose their protective barrier, and CDI can develop quickly with exposure to spores. The most commonly associated factor of microbiome disruption is antibiotic use, with decreases in the gut microbiota diversity detectable within days of antibiotic use. Ribaxamase is an orally ingested enteric-coated enzyme that destroys select β-lactams, including penicillins and cephalosporins, in the distal intestine. Antibiotic destruction in the intestinal space allows for protection of the host microbiome and reduces CDI risk. Two open-label, randomized phase 2a studies of intravenous (IV) ceftriaxone alone or with oral ribaxamase enrolled subjects with functioning ileostomies demonstrated that ribaxamase was well tolerated and fully degraded ceftriaxone to below the level of detection in the chime, with no effect on ceftriaxone plasma pharmacokinetics. A phase 3 study is expected to start the second half of 2019 to assess the efficacy and safety of ribaxamase in a broader patient population by including additional IV β-lactams with ceftriaxone and by enrolling patients with a variety of underlying infections. Pending phase 3 trial results, ribaxamase could be the first drug on the market for CDI prevention, making it one of the most novel drugs in the pipeline for CDI. Protecting the gut microbiota from the damaging consequences of antibiotics initially, rather
than trying to restore the microbiome after the damage has already been done, is game-changing in the CDI paradigm. Ridinilazole (formerly SMT19969) is a nonabsorbable antibacterial with a unique mechanism of action of elongating the _Clostridium difficile_ cell and inhibiting sporulation.15 In a phase 2 trial, ridinilazole was noninferior to vancomycin (15% noninferiority margin; _P_ = .0004), with sustained clinical response rates of 24/36 (66.7%) and 14/33 (42.4%) for patients on ridinilazole and vancomycin, respectively.16 Based on these results, investigators are conducting phase 3 studies to evaluate ridinilazole 200 mg orally twice daily compared with standard-dose vancomycin.

**NOVEL AGENTS IN EARLY DEVELOPMENT**

DS-2969b is a novel GyrB inhibitor.17 A low propensity for in vitro resistance development and limited impact on the intestinal microbiome were noted in studies.18,19,20 With the phase 1a studies just recently published, whether the company will decide to pursue phase 2 trials is unclear, but a drug with low propensity for resistance development and low impact on microbiome would be a critical step forward and would be expected to improve CDI recurrence and, thereby, reduce readmissions and overall cost to health care. We are looking forward to future similar drug developments.

RBX2660 is a commercially prepared, standardized, fecal microbiota suspension preparation that is packaged into a single-administration, ready-to-use enema bag. Clinical trials have evaluated its efficacy in patients with >2 CDI recurrences, with overall efficacy reported at ~90%. With FMT not FDA approved and uncertainty of long-term implications, rigorous unbiased clinical trials will shed further light on its use in patients with >2 recurrences.

Compared with the currently available CDI treatments, the novel drugs mentioned in this article may offer various advantages. However, because these new compounds are in early development, limited conclusions can be drawn until phase 3 clinical trials are completed and analyzed. Unfortunately, although current options for CDI drug development are exciting, we are simultaneously seeing major failures in the clinical trial development and management of CDI. The recent clinical failures of cadazoloid and surotomycin may be the product of poor study design, not poor drug effectiveness.

**LEARNING FROM CADAZOLID AND SUROTOMYCIN**

Cadazolid and surotomycin are 2 late-stage agents for CDI that recently failed meeting their clinical trial end points. Close analysis of these clinical trials suggests that poor end point definitions or poor study design may have resulted in trial failure—a costly mistake for a therapeutic area with significant medical need.

Cadazolid (ACT-179811) is a nonabsorbable, narrow-spectrum agent. A phase 2 multicenter, randomized, controlled study of various cadazolid dosages compared with those of vancomycin did not meet its end point because of strict definitions of diarrhea and cure.7,12 The clinical cure rates were not significantly higher than the preset 75% cure rate in any cadazolid group (68.4%-80.0%) or in the vancomycin group (68.2%). This was the result of the stringent criteria (>2 semi-formed or formed stools [and no unformed bowel movements [UMBs]] for 2 consecutive days) that were selected for the definition of diarrhea resolution. Patients were considered clinical failures when the study definition of clinical cure based on fecal output was not met. However, when modified criteria comparable to those used in the phase 3 studies of fidaxomicin (≤3 UMBs for 2 consecutive days) were applied,13 the response to vancomycin in the present study was comparable to that in the recently completed phase 3 trials, and the modified clinical cure rates for cadazolid (84.2%-94.1%) were comparable to those for vancomycin (86.4%). Nevertheless, because the phase 2 trial results indicated that cadazolid demonstrated superiority to vancomycin for recurrence and sustained clinical cure, the drug was moved to phase 3 trials.22 Unfortunately, cadazolid failed to meet the primary end point in one of the phase 3 trials (IMPACT-2). In the phase 3 trials, the primary end point was clinical cure, defined as resolution of diarrhea (≤3 UMBs/day for at least 2 consecutive days) on study treatment and maintained for 2 days after the end of therapy with no further CDI therapy required. This definition may be too strict because a patient’s status change from 16 UMBs to 4 UMBs would be considered a clinical failure based on IMPACT-1 and IMPACT-2 definitions. The observation that vancomycin, a current clinical standard of care, failed to meet the primary end point in the phase 2 studies and that cadazolid failed to meet the primary end point in IMPACT-2 strongly suggests that the study definition of resolution of diarrhea was too strict and could potentially be changed to ≤3 UMBs daily, or a 75% decrease in stool volume for at least 2 consecutive days.

Surotomycin is a minimally absorbed lipopeptide agent with a microbiome-sparing approach. In the surotomycin phase 2 trials, the recurrence rate was 17.2% versus 35.6%, favoring high-dose surotomycin compared with vancomycin, respectively (_P_ = .035).23 The primary end point was resolution of diarrhea sustained through 2 days after CDI therapy ended and no need for additional antibiotics. Again, phase 3 clinical trials did not meet the primary end point of clinical cure. Clinical trial data suggested the use of surotomycin over vancomycin may have some clinical benefits, including decreased recurrence rates, but again, clinical trial design challenges likely resulted in type II error, in which a potentially valuable treatment option is lost when true benefits may have been seen. End point definitions and patient selection regarding testing methods used to establish both diagnosis and that of relapse/failure (polymerase chain reaction vs enzyme immunoassay vs cytotoxic assay) potentially contributed to the surotomycin phase 3 failure. The phase 2 and 3 studies had trial design differences. The inclusion criteria differed (phase 2 trial: ≥4 UMBs were required for inclusion; phase 3 trial: ≥3 UMBs), the definition of cure differed (phase 2 trial: defined as <4 UMBs per 24-hour period for at least 2 consecutive days; phase 3 trial: ≤2 UMBs per 24-hour period for at least 2 consecutive days), and the follow-up period differed, potentially leading to distinct sustained clinical response rates (phase 2 trial: 28 days; phase 3 trial: 30-40 days). In both the phase 2 and phase 3 surotomycin trials, CDI diagnosis required only 1 toxin-positive result. The most current CDI diagnosis recommendations include a 2-step procedure. Critical clinical trial lessons must be learned from future studies, or other valuable treatment options will be lost. We also strongly urge clinicians to consider preventive care rather than chasing CDI after it already occurs, as limiting antibiotic use and preserving the microbiome is crucial to decreasing the public health threat of CDI.

References are available at ContagionLive.com.
With the Opioid Epidemic, Communities See Dramatic Increases in Infectious Diseases

Rising incidence of viral and bacterial infections has accompanied the opioid crisis, but it also presents new opportunities for multidisciplinary treatment and preventive care.

BY HERMIONE HURLEY, MD, MBCHB; ALIA AL-TAYYIB, PHD, MSPH; AND SARAH E. ROWAN, MD

(continued from cover page)

people who inject drugs (PWID) are at particularly high risk for acquiring blood-borne infections and differ in their risk behaviors from older people who inject. In a sample of individuals with opioid prescription misuse in Florida, the younger participants, aged 18 to 24 years, were significantly more likely to inject (odds ratio [OR], 8.4; 95% CI, 4.3-16.2) and more likely to reuse a syringe (OR, 3.2; 95% CI, 1.3-7.8) compared with those 45 years or older.12

The risk of acquiring blood-borne viruses may be particularly high for people injecting prescription opioids because the agents are not easily dissolved in water compared with powdered heroin, so more steps are required to prepare and apportion the drug for injection.13-16 Moreover, the population prevalence of young people aged 15 to 29 years who inject increased between 1996 and 2002 and continued to increase through 2007.17,18

VIRAL AND SERIOUS BACTERIAL INFECTIONS AND INJECTION DRUG USE

Hepatitis C virus (HCV) is the infection most closely linked to increases in injection drug use and accounts for more deaths in the United States than all other reportable infections combined.19 A dramatic decline in acute HCV cases occurred after blood supply screening began in the 1990s, but the past decade has seen an abrupt reversal of that trend, with the majority of new cases occurring in individuals aged 20 to 30 years20-21 (Figure).

Infections with hepatitis B virus have also increased among PWID, although the numbers are smaller than those for HCV. Many states are in the midst of outbreaks of hepatitis A among homeless populations and individuals using drugs. This represents a significant shift for a disease that was traditionally associated with restaurants and day care facilities.22
The association between HIV and injection drug use has been recognized since the beginning of the HIV epidemic, but HIV prevention efforts have been targeted mostly at preventing sexual transmission of HIV. The increase in reported cases of HIV acquired through injection drug use necessitates a shift in prevention activities. For example, Scott County, Indiana, saw an outbreak of more than 200 cases of HIV acquired through sharing of drug injection equipment; 90% of those individuals with newly diagnosed HIV were coinfected with HCV. Clusters of HIV among PWID have also been reported in urban settings such as Seattle, Washington, although the burden of disease has disproportionately affected rural communities that may not have easy access to harm reduction services such as syringe access programs and opioid agonist treatment.

Of significant concern is the increase in serious bacteremia and its sequelae. North Carolina saw a 12-fold increase from 2000 to 2015 in hospitalizations for endocarditis among individuals with a drug dependence diagnosis. Review of national data sets has revealed nationwide increases in admissions for injection drug use–associated endocarditis, with affected individuals being younger and more often female than traditional cohorts, who were more often male. Increases in soft tissue, bone, and joint infections among PWID have been reported as well. Deep tissue and valvular bacterial infections require prolonged periods of antibiotic therapy, often prompting weeks to months of hospital admission.

**OPPORTUNITIES TO INCREASE TREATMENT AND PREVENTION**

Infectious disease (ID) and substance use disorders (SUDs) have a bidirectional causal relationship. By incorporating elements of SUD and ID care, clinicians can increase completion of antibiotic treatment, go upstream to reduce life-threatening endocarditis or deep tissue infections, and increase rates of vaccination for preventable disease. ID treatment providers can rapidly obtain use treatment skills and easily adopt them to improve clinical outcomes. Motivational interviewing is a client-centered counseling style that promotes behavior change by maintaining rapport while allowing individuals to identify their own goals for lifestyle modifications. It has 4 principles: expressing empathy while avoiding arguing, developing discrepancy, rolling with resistance, and supporting self-efficacy. All staff in a clinic can use motivational interviewing techniques to promote medication adherence, increase the likelihood that patients will return for follow-up, allow incremental action toward sobriety, and reduce the number of times substances are injected.

Providing naloxone to patients with opioid use disorders will increase the chances they are alive to engage in their health care. Clinicians should make every appointment or admission an opportunity to offer education about harm-reduction activities, like single use of sterile syringes, avoidance of shared equipment, and use of test strips to check for unintended opioids like methamphetamine cut with fentanyl. Providers should also offer vaccination for preventable disease and HIV prophylaxis for people with unknown or discordant injecting and sexual partners.

Effective medications to reduce substance-related death and increase ongoing engagement in care are available. Clinicians can administer many medicines in an office-based setting or start them during a hospital admission. Prescription of buprenorphine requires an X waiver addition to an existing Drug Enforcement Administration license; providers can obtain this either online or by attending an in-person course. Naltrexone in oral or injectable form does not require additional licensing and is an effective adjunct to counseling for alcohol and opioid use disorders. Professional relationships with specialized substance clinics in clinicians’ regions can support efforts and allow easier referral for an individual who requires a higher level of care.

Clinicians working in ID are already aware of the negative effect of stigma. Promote and use the descriptor "PWID" rather than "intravenous drug user," and a person with substance use disorder rather than "addict." Individuals with substance use disorders anticipate judgment and carry shame in excess. If they experience interactions that make them feel welcome, they will be more likely to return for ongoing care.

**CONCLUSIONS**

The increasing morbidity and mortality from opioid and other substance use disorders are a call to action, and ID providers have a significant role to play. Rates of HIV, viral hepatitis, and life-threatening bacterial infections are increasing in US communities. By incorporating elements of ID and substance use treatment, clinicians can improve outcomes and increase satisfaction in the workplace. As ID providers, they can assist people with substance use disorders, and participation in their care can be a very rewarding experience.

References are available at ContagionLive.com.
Rapid ART Initiation: A New Model Presents Unique Opportunities and Challenges

Patients with a new diagnosis of HIV may benefit from rapid start of ART.

BY WILLIAM R. SHORT, MD, MPH, AAHIVS

Tremendous research and work over the past decades have transformed HIV infection from a once inevitably fatal condition to one that is both chronic and manageable in areas with access to antiretroviral therapy (ART). Despite these undeniable successes, the problem is far from being resolved even in regions with full access to ART. Recent US estimates indicate that 85% of people with HIV have been given a diagnosis, 62% have received medical care, 48% have been retained in care, and 49% of those in care have achieved virologic suppression. Although these estimates represent an increase compared with previous years’ figures, they nevertheless demonstrate that the medical community is far from achieving the 90-90-90 treatment target set by the Joint United Nations Programme on HIV/AIDS. The target indicates that by 2020, 90% of all people living with HIV should be aware of their status, 90% of those with a diagnosis should be receiving ART, and 90% of those receiving ART should achieve viral suppression. The US Department of Health & Human Services (HHS) has defined the key components of ending the HIV epidemic, and one of the strategies is to treat HIV infection rapidly and effectively to achieve sustained viral suppression.

The question that baffled investigators for years had been when to start ART, and findings from the START and TEMPRANO studies provided answers. The remaining question is how quickly to start ART once a diagnosis has been confirmed. Historically, a clinician would order a series of baseline lab tests, including an HIV genotype, which could take a few days to several weeks to return, in addition to participating in multiple counseling sessions prior to commencing ART. This model could disrupt the HIV care cascade, with the potential for patients not to be retained in care. Very high attrition rates have been noted for the period between testing and ART initiation, with estimates that one-quarter to one-third of individuals are lost to follow-up during this time. This has prompted investigators to attempt to address whether rapid initiation of ART is feasible and can help decrease the number of patients who are lost to follow-up.

CLINICAL TRIALS

Results of 3 randomized controlled trials (RCTs) conducted in resource-limited settings (Haiti, South Africa) demonstrated that earlier initiation of ART was associated with higher rates of early virologic suppression. In addition, Ward 86 in San Francisco, California, to which HIV testing sites refer patients, offered same-day or next-day intakes and received multidisciplinary evaluation, support, and insurance enrollment as it provided additional support for rapid initiation of ART.

An unblinded, randomized trial of standard ART initiation versus same-day HIV testing and ART initiation was conducted among outpatients at the Haitian Group for the Study of Kaposi’s Sarcoma and Opportunistic Infections clinic in Port-au-Prince, Haiti. The primary end point was retention in care, defined as 1 clinic visit between 12 and 15 months after HIV testing, with HIV-1 RNA <50 copies/ml at 12 months after testing. Participants were
randomly assigned 1:1 to standard ART initiation, defined as 3 weeks after HIV testing, or same-day initiation, defined as ART on the day of testing. A total of 762 participants were enrolled between August 2013 and October 2015, of whom 59 were transferred to other clinics for care and were excluded from the protocol, leaving 356 participants in the standard group and 347 in the same-day group. At the end of 12 months, significantly more patients remained in care and had achieved HIV-1 RNA <50 copies/mL in the same-day group compared with the standard-of-care group (53% vs 43.8%, P = .008). In addition, mortality was higher in the standard ART group (5.6% vs 2.9%, P = .033).7

RapIT was an unblinded RCT of single-visit ART initiation in 2 public health sector clinics in South Africa. Nonpregnant adults (>18 years) who received a positive HIV test or a first treatment–eligible CD4 count were randomized to standard or rapid initiation. Patients in the rapid initiation arm received a point-of-care (POC) CD4 count, and those who were ART eligible received POC tuberculosis testing if symptomatic, POC blood tests, a physical examination, education, counseling, and ART dispensing. Patients in the standard arm followed standard clinic procedures, which included 3 to 5 clinic visits over 2 to 4 weeks prior to ART dispensing. The primary outcome was viral suppression, defined as initiated, retained in care, and virally suppressed (<100 copies/mL within 10 months of study enrollment). A total of 377 patients were enrolled between May 8, 2013, and August 29, 2014. In the rapid arm, 119 of 187 (64%) patients initiated treatment and were virally suppressed at 10 months compared with 96 of 190 (51%) in the standard arm (relative risk, 1.26 [1.05–1.50]).8

CASCADE was a RCT in Lesotho, South Africa, that investigated the utility of home-based HIV testing and same-day ART initiation and its impact on linkage to care and viral suppression. Patients were randomly assigned to same-day, home-based ART initiation (n = 138) and subsequent follow-up intervals of 1.5, 3.0, 6.0, 9.0, and 12.0 months after treatment initiation at a health care facility or to usual standard of care (n = 140) with referral to the nearest health care facility for counseling followed by ART initiation and monthly follow-up visits after enrollment. The primary outcome was the rate of linkage to care within 3 months and viral suppression (defined as HIV-1 viral load <100 copies/mL) at 12 months from 11 through 14 months after enrollment. Within the first 90 days, significantly more patients were linked to care in the same-day group compared with the standard-of-care group (68.6% vs 43.1%, P < .001). In addition, more patients achieved viral suppression by 12 months in the same-day group (50.4% vs 34.3%, P < .007).9

San Francisco General Hospital launched the Rapid ART Program for Individuals with an HIV Diagnosis (RAPID) program in July 2013, designed to facilitate ART initiation for patients with a new HIV diagnosis by immediately addressing structural barriers to same-day treatment. Under this program, clinicians will initiate ART as soon as possible after HIV status is disclosed and ideally on the same day patients are referred for care. Of 86 patients with a new HIV diagnosis referred for initiation, 39 were managed according to the RAPID intervention and 47 received standard care. In addition, 35 of 39 (92.7%) of patients who were offered ART received it at their first visit in the clinic, and 37 of 39 (94.9%) started within 24 hours. Within 30 days after the initial clinic visit, 100% of patients in the RAPID group had initiated ART compared with 68% of patients receiving standard care of ART. The median time to viral suppression (HIV viral load <200 copies/mL) in patients in RAPID was 56 days from clinic referral compared with 79 days among those receiving standard care (P = .009).10

**CONSIDERATIONS FOR IMPLEMENTATION**

Rapid initiation of ART is important for several reasons. First, it optimizes the health of individuals with HIV. Secondly, strong scientific evidence from 2008 to 2016 demonstrates that individuals who receive ART and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others. These data have shown no linked HIV transmissions after >100,000 condomless sex acts in both female–male and male–male serodifferent couples in which the partner with HIV had an undetectable viral load.11 The Centers for Disease Control and Prevention and other organizations have endorsed the undetectable = untransmittable concept and noted that it is linked with ART initiation as soon as possible after diagnosis. Finally, rapid initiation may improve equity and accessibility of ART for people who may otherwise be lost to follow-up prior to commencing ART. **TABLE 1** highlights the recommendations for rapid ART by the guideline committees that clinicians use to assist in managing ART. The IHS guidelines call same-day initiation of ART investigational but state that it may be feasible and could potentially improve outcomes.12 The International Antiviral Society–USA (IAS-USA) guidelines recommend starting ART as soon as possible, including immediately after diagnosis. The only reason not to would be if the patient is not ready. In addition, the IAS-USA guidelines suggest avoiding nonnucleoside reverse transcriptase inhibitors because of concerns about transmitted drug resistance. Dolutegravir/tenofovir alafenamide (TAF) (or tenofovir disoproxil fumarate [TDF])/emtricitabine (or lamivudine) or bicapritav/TAF/emtricitabine or boosted darunavir TAF (or TDF)/emtricitabine is recommended for rapid initiation.13 Several barriers can prevent the implementation of a rapid-start program, including reluctance of clinicians to prescribe ART with minimal or no laboratory data available as well as unavailability of same-day clinic appointments for patients. Patients presenting with certain opportunistic infections may require a delay in starting ART, as outlined in **TABLE 2**, and they may be inappropriate for rapid ART.14

**CONCLUSIONS**

Staging ART on the day of an HIV diagnosis or at the first appointment is safe and well tolerated even before labs are obtained, and clinical trials have demonstrated its effectiveness. In addition, immediate ART leads to earlier viral suppression and may increase retention in care. Further research is needed on the best implementation strategies to support rapid ART initiation.15

References are available at ContagionLive.com.
Evaluating the Role of New β-Lactam Agents for Uncommon Pathogens

Novel β-lactam/β-lactamase inhibitor combinations and cefiderocol may play a part in the treatment of infections caused by Stenotrophomonas maltophilia, Achromobacter xylosoxidans, and Burkholderia cepacia complex.

BY SARAH L. SPITZNOGLE, PHARMD; AND SAMUEL L. AITKEN, PHARMD, MPH, BCIDP

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Patients with cystic fibrosis (CF) are at an elevated risk for chronic infections and morbidity. According to the 2017 Cystic Fibrosis Patient Registry, which provides comprehensive data on nearly 30,000 patients with CF, S maltophilia was identified in 12.9% of patients, A xylosoxidans in 5.7%, and Burkholderia cepacia complex in a further 2.5%. Patients with cancer, specifically those with a hematologic malignancy, are also at heightened risk for infections with these organisms. Infection with S maltophilia can have devastating complications in patients with a hematologic malignancy, for which mortality approaches 100% in patients with hemorrhagic pneumonia.

These pathogens share many features, including their environmental origins, ability to cause persistent infections due to biofilm formation, and intrinsic multidrug resistance, specifically to most β-lactam agents. Although other antimicrobials, particularly trimethoprim/sulfamethoxazole, later-generation tetracyclines, and fluoroquinolones, may be active in vitro and have clinical utility, emerging resistance and concerns over toxicity and efficacy in serious infections highlight a potential role for the newly available β-lactam/β-lactamase inhibitor combinations ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam, and ceftolozane/tazobactam. In this short review, we describe the mechanisms of β-lactam resistance for S maltophilia, A xylosoxidans, and Burkholderia spp and demonstrate how understanding the mechanistic basis of resistance is necessary to define the role of β-lactam/β-lactamase inhibitor combinations against these organisms. We additionally summarize clinical data on their use.

**STENOTROPHOMONAS MALTOPHILIA**

*Stenotrophomonas maltophilia* is an intrinsically carbapenem-resistant organism and is the leading carbapenem-resistant pathogen isolated from patients with hospital-acquired and ventilator-associated pneumonia. Trimethoprim/sulfamethoxazole is the current drug of choice; however, resistance is increasingly described, and its utility is limited in patients with hematologic malignancy and transplant recipients because of concerns for myelosuppression and nephrotoxicity. The characteristic β-lactam resistance profile of *S maltophilia* is achieved through the production of 2 chromosomal, inducible β-lactamase enzymes: L1, an Ambler class B metallo-β-lactamase, and L2, an Ambler class A serine β-lactamase. L1 has a substrate profile similar to that of other metallo-β-lactamas and hydrolyzes all commercially available β-lactamases, with the exception of aztreonam, and is not inhibited by commercially available β-lactamase inhibitors. L2 is a relatively narrow-spectrum cephalosporinase that hydrolyzes most cephalosporins and aztreonam but has no activity against carbapenems. L2 is inhibited by clavulanate but is generally not inhibited by the sulfone β-lactamase inhibitors sulbac tam and tazobactam.

When both enzymes are expressed in combination, most β-lactams are eliminated as therapeutic options for *S maltophilia*, and commercially available β-lactam/β-lactamase inhibitors have no added activity. Results from surveillance studies indicate similar resistance profiles for ceftazidime and ceftazidime/avibactam, meropenem and meropenem/vaborbactam, and imipenem and imipenem/relebactam (Table online). One approach to overcoming β-lactam-mediated resistance is to employ a combination of aztreonam, which is not hydrolyzed by L1, and avibactam, which inhibits L2. Mojica et al evaluated the combination of aztreonam and avibactam against 27 clinical isolates of aztreonam-resistant *S maltophilia* and found that the combination restored activity in 23 of 27 isolates. These findings have been confirmed by others. Because aztreonam/avibactam is not commercially available, the combination of ceftazidime/avibactam and aztreonam has been used clinically. This triple-drug combination was used to successfully treat a renal transplant recipient...
with refractory *S. maltophilia* bacteremia. Recent whole-genome sequencing evaluations of *S. maltophilia* suggest that L1 and L2 are subject to a high degree of interstrain variability with implications for β-lactam substrate specificity and inhibitor profile. Additional in vitro surveillance and clinical data are needed before this combination can be broadly recommended, though the ability of most clinical microbiology laboratories to test for activity of this combination is limited. The combination of aztreonam and clavulanate has similar activity to aztreonam and avibactam, but as no intravenous formulation of clavulanate is available commercially in the United States, the therapeutic potential of this synergy is limited.

Although rebekactam is structurally similar to avibactam, it appears to be a less potent inhibitor of L2 than avibactam, with a half-maximal inhibitory concentration of 470nM against L2 relative to 15nM for avibactam. No data have been published for the boronic acid inhibitor vaborbactam. Ceftolozane/tazobactam has activity similar to that of ceftazidime and lacks additional activity against ceftazidime-resistant strains of *S. maltophilia*.

**ACHROMOBACTERXYLOSOXIDANS**

Although several members of the genus *Achromobacter* have been described as causing infections in humans, *A. xylosoxidans* is the most common and well described. *A. xylosoxidans* is intrinsically resistant to aztreonam and most cephalosporins, whereas piperacillin/tazobactam and the carbapenems, including meropenem and tazobactam, are both essentially inactive against the desired piperacillin/avibactam combination. No literature on the clinical utility of this combination is currently available. No published data are available on the potential utility of other novel β-lactamase inhibitors against *B. cepacia* complex infections. Ceftolozane/tazobactam activity has variable activity against *B. cepacia* complex members and does not add appreciable activity in ceftazidime-resistant strains.

**BURKHOLDERIA SPECIES**

The genus *Burkholderia* includes several clinically relevant organisms, including the *B. cepacia* complex, *Burkholderia mallei*, and *Burkholderia pseudomallei*. Members of the *Burkholderia* genus possess a large genome with multiple chromosomessomes, which leads to genetic plasticity and multiple antimicrobial resistance determinants. *Burkholderia pseudomallei*, the causative agent of melioidosis, is not found in the United States, and *B. mallei*, the cause of glanders, is largely of historical concern. Therefore, these organisms are not further discussed. The *B. cepacia* complex species, consisting of *B. cepacia*, *Burkholderia cenocepacia*, *Burkholderia multivorans*, and others, are predominantly pathogens in patients with CF but have been described in other patients, particularly those with chronic granulomatous disease. In addition to intrinsic resistance to penicillins and narrow-spectrum cephalosporins, *Burkholderia* spp are intrinsically resistant to the polymyxins through alterations in lipid A, which lead to changes in net lipopolysaccharide charge and decreased polymyxin binding affinity. *Burkholderia* spp produce numerous efflux pumps, including at least 6 RND-type efflux pumps in the *B. cepacia* complex. β-lactam resistance in *B. cepacia* complex is mediated predominantly through 2 chromosomal β-lactamase enzymes, a broad-spectrum, Ambler class A carbapenemase (either PenB in *B. cepacia* or PenA in *B. multivorans*), and AmpC-like enzymes that hydrolyze penicillins, extended-spectrum cephalosporins, and carbapenems. Both enzymes are inducible through an ampD-controlled mechanism similar to other gram-negative organisms with chromosomosomal, inducible AmpC β-lactamases. As these enzymes are not constitutively expressed, β-lactams, particularly ceftazidime and meropenem, are frequently active against *B. cepacia* complex. However, when PenA or PenB is expressed, *B. cepacia* complex species become resistant to extended-spectrum cephalosporins and carbapenems. Efflux pumps, particularly RND-3 pumps, also appear to have a role in resistance to ceftazidime and meropenem. Similar to other class A enzymes, avibactam is a potent inhibitor of PenA in *B. multivorans* and can restore in vitro activity against ceftazidime-resistant strains. Ceftazidime/avibactam has been used successfully in the treatment of a 2-month-old child with refractory *B. cepacia* complex bacteremia who had failed both ceftazidime and meropenem, as well as in a small case series of 4 patients with cystic fibrosis colonized with extensively drug-resistant *Burkholderia* spp.

Despite promising in vitro activity and successful use in a small number of patients, the activity of ceftazidime/avibactam against *B. cepacia* complex is highly variable. Against extensively drug-resistant isolates, a novel quadruple-drug combination of ceftazidime/avibactam and piperacillin/tazobactam has shown promising activity. The mechanism appears to be dependent on slow hydrolysis of piperacillin by AmpC and inhibition of PenA by avibactam, and therefore, ceftazidime and tazobactam are simply “bystanders” to the desired piperacillin/avibactam combination. No literature on the clinical utility of this combination is currently available. No published data are available on the potential utility of other novel β-lactamase inhibitors against *B. cepacia* complex infections.

**CEFIGEROCOL**

Cefiderocol, a novel siderophore cephalosporin, is stable against hydrolysis by both serine and metallo-β-lactamases. Mechanistically, cefiderocol chelates ferric iron and is transported across the outer membrane and into the periplasmic space, where it binds to penicillin binding protein 3. Against a collection of North American and European gram-negative organisms, cefiderocol demonstrated potent in vitro activity against *S. maltophilia* (minimum inhibitory concentration [MIC] ≤ 0.5 μg/mL; 100% sensitive at a provisional breakpoint of ≤ 4 μg/mL) and was active against 11/12 *Burkholderia* isolates at MICs ≤ 1 μg/mL, with a single isolate having a MIC of 16 μg/mL. Activity of cefiderocol against *S. maltophilia* and *Burkholderia* was again seen in a collection of gram-negative isolates from a Comprehensive Cancer Center in the southern United States, in addition to observed activity against *Achromobacter* spp. To date, no published clinical data are available on the utility of cefiderocol against these organisms, and the compound is not by the US Food and Drug Administration. In vitro data suggest that cefiderocol is a potentially promising option against these problem pathogens.

**SUMMARY**

A knowledge of the molecular mechanisms of β-lactam resistance is crucial to understanding the potential utility, or lack thereof, of novel β-lactams/β-lactamase inhibitors against less common non–lactose-fermenting gram-negative organisms. These associations can be extended to *Achromobacter* spp, in which intrinsic resistance to cephalosporins and carbapenems is due to efflux pumps, and accordingly novel β-lactam/β-lactamase inhibitors are inactive. In *S. maltophilia*, an intrinsic cephalosporinase and metallo-β-lactamase confer resistance to novel β-lactam/β-lactamase inhibitors, although the addition of aztreonam to avibactam overcomes this resistance. Lastly, *Burkholderia*, which expresses a class A carbapenemase and AmpC-type enzyme, is generally sensitive to ceftazidime/avibactam and in combination with piperacillin/avibactam appears to restore activity against some resistant isolates. As these organisms are poorly studied, further in vitro and clinical data are needed to validate the potential clinical role of these novel agents.

References and table are available at ContagionLive.com.
“Antibiotic Never Events”: The Ideal Target to Reduce Antimicrobial Exposure

By stopping unnecessary antibiotics before they start, clinicians can avoid unnecessary harm to the patient and the population.

BY BRADLEY LANGFORD, PHARMD, BCPS; JENNIFER LO, PHARMD; AND KEVIN SCHWARTZ, MD, MSC, FRCPC

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However, with the pressing global threat of antimicrobial resistance, consideration of the highest-yield activities that maximally reduce the quantity of antibiotic exposure is of critical significance. For example, reducing duration of therapy or using a narrower-spectrum antibiotic will reduce the risk of antibiotic resistance, Clostridioides difficile infection, and adverse effects, but if the patient has a noninfectious condition, the highest-yield approach to reducing collateral damage is avoiding antibiotic use in the first place. When no benefit of antibiotic use exists, any harm is unnecessary and avoidable.

Antimicrobial stewards will recognize the multitude of noninfectious conditions that often receive unnecessary antibiotics, including blood culture contamination, colonized wounds, cellullitis mimics such as stasis dermatitis, and aspiration pneumonitis. However, more than 90% of antibiotics are used outside hospitals, with 2 of the most common reasons for unnecessary antibiotic use being asymptomatic bacteriuria (ASB) and viral upper respiratory tract infection (URTI). Antimicrobial stewardship leaders have described these conditions as antibiotic never events (ANEs). The term never events was introduced in 2001 to describe severe medical errors that should never occur and are largely preventable.

Experts have suggested that the field of antimicrobial stewardship borrows this terminology and uses the term antibiotic never events to address the appropriateness of antibiotic prescribing. We aim to review these 2 key ANEs, describe challenges, and list key strategies that clinicians can employ to prevent unnecessary antimicrobial exposure for their patients.

TWO KEY ANES: ASB AND VIRAL URTI

Asymptomatic bacteriuria

ASB is the presence of bacteria in the urine without signs or symptoms attributable to urinary tract infection (UTI). The prevalence of ASB can be as high as 15% to 50% in older adults and as high as 100% in those with chronic indwelling urinary catheters. Aside from treatment for 2 populations—patients who are pregnant and those undergoing urological procedures expected to cause mucosal trauma—overwhelming evidence shows that treating ASB with antibiotics is not beneficial and can lead to harm, including increased risk of adverse effects and antimicrobial resistance. Positive urine cultures are often unjustly deemed to be indicative of UTIs in patients with nonspecific symptoms (eg, delirium or foul-smelling or cloudy urine) and, as such, are identified as major targets for antimicrobial stewardship programs in long-term care and acute care to reduce unnecessary antibiotic use.

Viral Upper Respiratory Tract Infections

In outpatient settings, a large proportion of patients with acute upper respiratory tract infections receive antibiotic prescriptions despite their likely viral etiology. Sinusitis, bronchitis, and acute pharyngitis are typically viral infections and are 3 of the main reasons for antibiotic misuse in primary care. In fact, up to half of antibiotic prescriptions for upper respiratory tract infections have been determined to be unnecessary.
REASONS FOR UNNECESSARY ANTIBIOTICS AND STRATEGIES TO PREVENT THEIR USE

Antibiotic prescription decisions are complex. In addition to lack of knowledge or awareness of evidence, some other factors commonly cited as reasons for antibiotic overuse are:15,16

• **Fear of harm:** Concerns about antibiotic under-treatment harms (recurrence, increased severity) often trump those of overtreatment (adverse effects, antibiotic resistance, C difficile infection).

• **Externalized responsibility:** Prescribers may believe the harms of antibiotic therapy are more likely caused by other clinicians in other settings, distant from their own.

• **Balancing of risks:** Immediate risk to the patient is weighted heavily over less tangible delayed risks to the patient and the population.

• **Diagnostic uncertainty:** Clinicians will err on the side of caution by prescribing antibiotics in uncertain situations, thereby reducing cognitive effort associated with differential diagnoses.

• **Perceived demand:** Pressure from patients and family may be real or perceived, and the concern that non-prescribing can reduce patient satisfaction.

Strategies to prevent unnecessary use should take into account the known barriers associated with overuse behavior. The drivers of unnecessary antibiotic use are frequently emotionally salient to both the patient and prescriber. Antimicrobial stewardship strategies, on the other hand, are inherently less emotionally salient.14 Therefore, strategies must use the principles of behavioral science by addressing the emotional aspect of prescribing, the environmental context in which prescribing decisions are made, and factors related to prescribers’ capability, opportunity, and motivation to change their behavior.15 For these reasons, education alone is typically insufficient to improve antibiotic prescribing.

The following are a few well-supported strategies to prevent antibiotic never events.

**Peer Comparison**

Audit and feedback with peer comparison have been shown to be more effective than traditional approaches for behavioral change. They can be helpful for reducing prescribing variability and targeting outlier prescribers by illustrating the difference in their antibiotic prescribing practice compared with that of their peers.16 Peer comparison uses behavioral strategies of persuasive communication and social normative feedback that have been shown to nudge prescribers to prescribe fewer antibiotics without causing harm.17 Two recent randomized, controlled trials in outpatient settings have found that providing social normative feedback on antibiotic prescribing resulted in a significant decrease in prescribing.18,19 For those looking to implement audit and feedback, Brehaut and colleagues presented 15 practical strategies to improve impact, including frequency of feedback provision, choice of comparators, and use of actionable messaging.20

**Communication Techniques**

Shared decision making involves conversations between the prescriber and the patient. It is facilitated by eliciting patient expectations and providing information on the benefits and risks of therapy and their expected frequency of occurrence. This approach has been shown to reduce inappropriate antibiotic prescribing for URTIs while maintaining patient satisfaction.21 Various decision aids and infographics are available to support this process.

Given the frequently cited concern that patients and family members demand antibiotics for indications that do not require them (e.g., ASB or viral URTIs), clinicians can follow additional techniques to address these challenging issues. Research on communication strategies has demonstrated the effectiveness of providing a positive treatment recommendation (“You can take a spoonful of honey to ease your sore throat and prevent cough”), as well as a negative treatment recommendation (“This infection is likely caused by a virus, so you shouldn’t take antibiotics because they won’t help”). This communication strategy results in shorter clinical visits, a lower likelihood of receiving an antibiotic prescription, and high family satisfaction.22

Tools such as viral prescribing pads that replace antibiotic prescriptions can be helpful in employing these negative and positive recommendations, thus ensuring patients feel satisfied despite not receiving an antibiotic. Likewise, resident and family letter templates can help to ensure that caregivers are aware of the harms of treating ASB with antibiotics and the contingency plans to improve patients’ symptoms (e.g., increased fluid intake, increased frequency of monitoring).

**Multifaceted Approaches**

A comprehensive program implemented in 10 long-term care homes in Ontario, Canada, used a multimodal approach to successfully prevent unnecessary urine culturing.23 The program incorporated key strategies for developing new policies and procedures, appointing local champions, providing education to staff and families, coaching, and process surveillance that were tailored to known challenges to reducing urine culturing. In addition to these strategies, formation of an implementation team and buy-in from staff and prescribers were noted to be key success factors. Five practice changes were employed: (1) discontinuing routine urine screening, (2) discontinuing the use of dipsticks for UTI diagnosis, (3) obtaining a urine culture only when residents have signs and symptoms of UTI, (4) obtaining a culture with proper technique to avoid contamination, and (5) recommending antibiotics only when clinical criteria are met. This program decidedly aimed at urine culturing to prevent the downstream consequences of reacting to a positive urine culture.23 The multimodal strategy was associated with a 28% reduction in urine culturing and a 40% reduction in urinary antibiotic use.24

**CONCLUSIONS**

Preventing unnecessary antibiotic treatment before it starts is a vital component of antimicrobial stewardship initiatives. Key high-yield opportunities include the prevention of antimicrobial never events, such as antibacterial treatment of viral URTIs and ASB. The drivers for antibiotic overuse are multifactorial, so solutions may need to be multifaceted to address known barriers to behavioral change. Effective evidence-based antimicrobial stewardship strategies to prevent unnecessary antibiotic use include peer comparison, patient communication strategies, and multifaceted educational and organizational initiatives.

References are available at ContagionLive.com.
In a recent Contagion® Peer Exchange panel, experts discussed considerations for antiretroviral therapy (ART) for women who are pregnant or of childbearing potential, the potential risks and benefits of changing ART regimens in patients with stably suppressed disease, and optimal monitoring of patients with undetectable = untransmittable (U = U) status.

**HIV TREATMENT OPTIONS FOR PREGNANT WOMEN**

W. David Hardy, MD, said women of childbearing potential can take most ART regimens and added that 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase inhibitor are effective for most patients, particularly if the combination includes tenofovir alafenamide. “Even the idea about having to use a boosted PI [protease inhibitor]...that’s gone away as well,” he said.

Eric S. Daar, MD, mentioned that although providers used to consider risks with ART only after women became pregnant, they have shifted their focus to include women of childbearing potential as well as pregnant women, after data from Botswana showed a 7- to 10-fold increase in risk for neural tube defects in babies of women who became pregnant while taking dolutegravir.1 According to Daar, the data from the Botswana cohort raised concerns about regimens for women of childbearing potential because the neural tube defects tended to occur in women exposed to dolutegravir at the time of conception.

“HIV Screening, Prevention, and Treatment Advances”

**MODERATOR**

Joseph Eron, MD
Professor of Medicine
University of North Carolina
School of Medicine, Chapel Hill

**PANEL**

W. David Hardy, MD
Adjunct Professor of Medicine,
Johns Hopkins University,
Baltimore, MD

Paul Sax, MD
Clinical Director, Division of
Infectious Disease, Brigham and
Women’s Hospital; Professor
of Medicine, Harvard Medical
School; Boston, MA

Ian Frank, MD
Professor of Medicine,
University of Pennsylvania
Perelman School of Medicine,
Philadelphia, PA

Eric S. Daar, MD
Interim Chair, Department of
Medicine, and Chief, Division of
HIV Medicine, Harbor–University
of California; Los Angeles (UCLA),
Medical Center; Professor of
Medicine, David Geffen School of
Medicine at UCLA

“I used to be the only time we had to worry about these drugs in pregnancy was for our subset of patients who were pregnant,” said Daar. “Now we have to worry about it for all our women of childbearing potential who aren’t reliably using contraception.”

However, Paul Sax, MD, said that the benefits of dolutegravir-based regimens may exceed the potential risks in women of childbearing potential. “You don’t want to deprive women of the best possible therapies,” he said. “Numerically, it’s a trade-off that is not easily answerable because the benefits to a woman going on the best regimen may exceed the risks of the neural tube defects, which are really right now a big unknown.”

Daar added that the signal for the increased risk for neural tube defects could go away with additional follow-up. Updated data from the Antiretroviral Pregnancy Registry presented at International Antiviral Society 2019: Conference on HIV Pathogenesis, Treatment, and Prevention reported a rate of 0.40%—which was much higher than the rate of 0.03% in women taking other ART therapies—but the panelists cautioned that the small number of women taking dolutegravir (248 patients) and the lack of data on how many were taking it at the time of conception prevent a definitive conclusion.2

Raltegravir in combination with a backbone of 2 NRTIs is recommended for ART-naive pregnant women with...
HIV and may be a good choice for women of childbearing potential, although Daar noted the low number of documented exposures at the time of conception. Sax added that although PIs such as darunavir are increasingly used during pregnancy, they can be difficult to tolerate because of gastrointestinal toxicities and a potential association with premature birth.

Moderator Joseph Eron, MD, concluded that a stable, well-tolerated regimen for most women should not be altered when they become pregnant unless it includes cobicistat because of the pharmacokinetic concerns associated with the drug.

**Dolutegravir/Rilpivirine Combination Therapy for HIV**

The panelists discussed indications for and potential benefits and risks of switching patients with virologic suppression to less toxic and complex regimens. Results of the phase III GEMINI-1 and GEMINI-2 trials showed noninferiority of dolutegravir/lamivudine compared with dolutegravir plus tenofovir disoproxil fumarate and emtricitabine. Sax said that because lamivudine has been available since 1995, its safety track record is well established, and it is cost-effective for patients who are stably suppressed. Additionally, dolutegravir/lamivudine may be a good option for patients with moderate to severe renal disease, said Sax.

“These typically are older patients—older patients who have maybe been on tenofovir for years in its [disoproxil fumarate] formulation,” Sax said. “Their creatinine clearance is 30 mL/min, and you want to save those last nephrons. Why not switch them to dolutegravir/lamivudine or even dolutegravir/emtricitabine if you’re concerned about using lamivudine with impaired renal function?”

Similarly, results of the phase III noninferiority SWORD-1 and SWORD-2 trials, which randomized patients with stable levels of HIV RNA on their first or second ART regimen to continue their current therapy or switch to dolutegravir/rilpivirine (available in a single-tablet combination pill), showed virologic suppression rates of 95% in both groups, suggesting that these patients could be switched to the single-tablet regimen safely, according to Ian Frank, MD. Frank stated that patients with renal insufficiency, complicated regimens with multiple baseline or new associated mutations, or a coverage gap in their Medicare drug plans may be good candidates for dolutegravir/rilpivirine.

“Dolutegravir/rilpivirine] isn’t cheaper, but I’ve had people who are on complicated boosted [PI] regimens with integrase inhibitors, really 5 individual antiretrovirals, who have been able to switch to this and simplify their regimen and cost saving,” Frank said.

Although the panelists cautioned that the exclusion of patients with transmitted resistance in the SWORD trials may prevent universal application of the findings, Eron noted that he has used the combination to simplify complicated regimens of patients with NNRTI and PI resistance mutations.

**The Difficulty of Switching ART Regimens in HIV**

Sax emphasized the importance of consulting with experts in HIV treatment before changing a patient’s ART regimen. “A lot of our patients are so stable now that they could be managed by primary care, general internists, family practitioners—people who are not HIV specialists,” said Sax. “But if you’re switching a regimen, get some input from [an expert].”

Hardy added that although the approval of new drugs provides more options for treatment, it may also add pressure for physicians to try a new regimen. “There has to be a good reason to switch,” he said. “I think that’s actually the important thing, and when you do make that decision and you have questions, particularly about previous treatment history, you really need to get help with that. Because you can make bad decisions and actually cause harm by switching.”

However, Frank pointed out that some patients who do not report adverse effects associated with efavirenz-based regimens feel better after switching to a regimen that does not contain efavirenz.

“I think it’s always worth talking to a patient who’s on an older combination to carefully discuss the presence of maybe some subtle symptoms that may be associated with that combination and [paying] careful attention to lipid levels, particularly on an efavirenz-inclusive, fixed-dose combination,” he said. “They’re on an older formulation of tenofovir with renal and potentially bone effects, so there are things to pay attention to. Although things aren’t broken, it doesn’t mean that things aren’t slowly deteriorating, and maybe a more modern, less toxic regimen is something to be considered.”

Although the panelists agreed that the goal is to give patients the simplest, safest therapy possible, Sax concluded that careful analysis of drug resistance tests is critical before making any switch. “The last thing we want to do is switch somebody and have them get resistance to a new drug class, especially integrase class,” he said.

**Recommended HIV Monitoring Approach for Stable Patients**

In the discussion about approaches for monitoring patients with U = U status, Frank stated that the frequency of monitoring depends more on their comorbidities than on their HIV infection.

“If people have undetectable viral loads and their CD4 counts are high, I usually don’t see people more frequently than every 6 months,” he said, although he stated that “I don’t want it to go too long before I see people.” He added that he checks viral loads and CD4 counts at each visit, even though such frequent monitoring of CD4 count in patients with U = U status is likely unnecessary.

“Unfortunately, it’s hard to convince my long-term patients that they don’t need to pay attention to their CD4 count,” said Frank. “But there’s clearly no need to do that. There’s absolutely no risk of CD4 counts falling.”

However, Frank said that frequent testing for sexually transmitted infections, including hepatitis C, is critical. He stated that individuals who are antibody negative should have annual hepatitis C testing and that patients who have been treated and cured of hepatitis C should have annual testing for hepatitis C RNA levels.

Additionally, Frank said that lipid levels should be checked annually according to Ryan White & Global HIV/AIDS Programs reporting and that renal function should be monitored because several ART drugs, such as next-generation integrase inhibitors, can have an effect on the distal renal tubular secretion of creatinine.

“With dolutegravir and bictegravir, we sometimes see a 0.1- or 0.2-mg/dL increase in creatinine,” said Frank. “I’m looking at urinalyses to make sure there isn’t protein or glucose in the urine, which would be a sign of renal tubular damage.”

However, the panelists debated whether the extensive battery of tests at such frequent intervals is necessary for patients with U = U status and few comorbidities, adding that these patients often do not see the purpose of such frequent monitoring. Sax suggested a randomized study comparing outcomes of guidelines-recommended frequency of testing versus testing based on age and comorbidities plus an annual viral load test.

“[Monitor patients] as it would be appropriate in a general medicine population,” said Sax. “I bet there wouldn’t be a difference in outcome. I have a lot of people who’ve earned a yearly visit because they’re so stable.”

However, Hardy pointed out that regular testing of CD4 counts and viral load often provides psychological benefits for the patient. “If you’re just [managing] HIV, the only thing you have to probably do is the CD4 count once a year, a viral load maybe twice a year,” he said. “Part of the time you do it because the patient wants to know it, because it does provide positive reinforcement to them—that their pill they’re taking every day is doing something. And I think that’s something that shouldn’t be discounted because [testing is] not that expensive.”

Sax concluded that although less frequent monitoring is likely safe for patients with long-term virologic suppression, clinicians should follow patients who just started therapy very closely, perhaps with visits every 2 to 4 weeks, until they have virologic suppression. “But now [virologic suppression] happens so quickly—it’s often just 3 visits or 4 visits, and they’re suppressed,” he said. ▲

References are available at ContagionLive.com.
ASCENT: Mosaic-Based Vaccine Induces High Immune Response Against Broad Range of HIV Subtypes

BY ALEXANDRA WARD, MA

Formulating a preventive vaccine for HIV-1 infection has proved elusive for investigators, who must contend with the diverse strains of the virus circulating the globe. But results from the ongoing phase 2a ASCENT study, which were presented at the 10th International AIDS Society Conference on HIV Science (IAS 2019), demonstrate that 2 investigational mosaic-based prophylactic vaccine regimens intended to prevent HIV-1 infection induced high immune responses against a broad range of virus strains.


In the randomized, double-blind, placebo-controlled ASCENT study, investigators sought to compare a bivalent combination of clade C and Mosaic gp140 with a single-valent clade C gp140. A total of 152 healthy adults (18-50 years, 59% female) in Kenya, Rwanda, and the United States were randomized to Ad26.Mos4.HIV at weeks 0 and 12 and Ad26.Mos4.HIV and aluminum adjuvanted gp140 Env protein (clade C gp140 250 µg or bivalent clade C/Mosaic1 gp140, each 125 µg) at weeks 24 and 48 or placebo.

Twenty-six participants received Ad26.Mos4.HIV and clade C gp140, and 100 participants received Ad26.Mos4.HIV and bivalent gp140. Twenty-six others received placebo.

Both active regimens were well tolerated and immunogenic, with no serious adverse events reported. Notably, bivalent gp140 produced enhanced immune responses to clade B, which is the prevalent subtype in the Americas, Western Europe, and Australasia.

“HIV Env-specific binding antibody levels and subclass distribution showed both regimens induced binding and functional antibodies to all antigens tested. Clade C responses were not attenuated by replacing half the clade C dose with Mosaic1 gp140, while clade B responses improved \( P < .05 \),” investigators reported.

“At week 28, similar PTE [potential T cell epitopes] Env ELISpot responses were observed, with medians of 444 and 452 SFU [spot-forming units]/10⁶ PBMC [peripheral blood mononuclear cells] in bivalent or clade C groups, respectively. CD4+ (but not CD8+) T-cell [intracellular cytokine staining] responses increased to Mos1 gp120 peptides in the bivalent relative to clade C group (0.147% vs 0.123% IL-2 and/or IFNγ [interferon γ]+ CD4 T-cells, 81% vs 50% response, respectively),” the research team concluded.

The ASCENT trial results support the use of bivalent clade C/Mosaic1 gp140 with Ad26.Mos4.HIV, which will be further studied in the recently announced Mosaic phase 3 study.

“This mosaic-based vaccine regimen is designed as a global vaccine with the goal of preventing infections from the wide range of viral strains responsible for the HIV pandemic,” Hanneke Schuitemaker, PhD, vice president and global head of viral vaccine discovery and translational medicine at Janssen Vaccines & Prevention B.V., told Contagion®. “Mosaico is planned to be a 3800-person study of men who have sex with men and transgender people. The study will be conducted across 3 continents, 8 countries, and over 55 clinical trial sites. Enrollment is expected to begin in the United States later in 2019.”

Mosaico is sponsored by Janssen Vaccines & Prevention, B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson, and supported by the National Institutes of Health’s National Institute of Allergy and Infectious Diseases. Additional partners include the HIV Vaccine Trials Network and the US Army Medical Research and Development Command.

The study, ASCENT: Phase 2a, Randomized, Double-Blind, Placebo Controlled Study Evaluating Safety and Immunogenicity of Two HIV-1 Prophylactic Vaccine Regimens Comprising Ad26.Mos4.HIV and Either Clade C gp140 or Bivalent gp140, was presented on Tuesday, July 23, 2019, at IAS 2019 in Mexico City, Mexico. ▲
Single dose ORBACTIV® can treat appropriate ABSSSI* patients without a required hospitalization

Single-dose ORBACTIV® (oritavancin) is an alternative to multi-dose vancomycin course of therapy for ABSSSI.1,2

Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients1,2

Pooled Clinical Data from SOLO I and SOLO II**3

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>ORBACTIV® N=978 % (n)</th>
<th>VANCOMYCIN N=981 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response at 48–72 hours (primary endpoint)§</td>
<td>81.2% (794)</td>
<td>80.9% (794)</td>
</tr>
<tr>
<td>Clinical success at 14–24 days (secondary endpoint)¶</td>
<td>81.2% (794)</td>
<td>80.2% (787)</td>
</tr>
</tbody>
</table>

§ Early clinical response defined as a composite of the cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug at 48–72 hours.

¶ Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms at post-therapy evaluation at day 14–24 and no further treatment with antibiotics was needed.

** mITT population; SOLO I and SOLO II were two identical, randomized, double-blind, non-inferiority Phase 3 trials comparing ORBACTIV® 1200 mg to vancomycin 1 g or 15 mg/kg twice daily for 7 to 10 days for the treatment of ABSSSI in 1959 patients.

Real Patient Case Study

John F – Diabetic with Cellulitis

This case study is an actual ABSSSI patient who was treated with a single 1200-mg dose of ORBACTIV®.

No additional treatments were given to the patient for this infection. Individual results may vary.

The treating physician is a paid consultant of Melinta Therapeutics, Inc.

Resolution of John’s cellulitis following single-dose ORBACTIV®

Prior to single-dose ORBACTIV® 1200-mg infusion

12 hours after ORBACTIV® infusion

48 hours after ORBACTIV® infusion

References:

Please see Brief Summary of ORBACTIV® Prescribing Information on following pages.
1. INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

ORBACTIV® (oritavancin) for Injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

- Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant isolates),
- Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group (includes S. anginosus, S. intermedius, and S. constellatus),
- Enterococci faecalis (vancomycin susceptible isolates only).

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORBACTIV® and other antibacterial drugs, ORBACTIV® should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4. CONTRAINDICATIONS

4.1 Intravenous Unfractionated Heparin Sodium

Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after ORBACTIV® administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours (5 days) after ORBACTIV® administration [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].

4.2 Hypersensitivity

ORBACTIV® is contraindicated in patients with known hypersensitivity to ORBACTIV®.

5. WARNINGS AND PRECAUTIONS

5.1 Coagulation Test Interference

ORBACTIV® has been shown to artificially prolong aPTT for up to 120 hours, PT and INR for up to 12 hours, and activated clotting time (ACT) for up to 24 hours following administration of a single 1200 mg dose by binding to and preventing action of the phospholipid reagents commonly used in laboratory coagulation tests. ORBACTIV® has also been shown to elevate D-dimer concentrations up to 72 hours after ORBACTIV® administration. For patients who require aPTT monitoring within 120 hours of ORBACTIV® dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered [see Contraindications (4.1) and Drug Interactions (7.2)]. ORBACTIV® has no effect on the coagulation system in vivo.

5.2 Hypersensitivity

Serious hypersensitivity reactions have been reported with the use of ORBACTIV®. If an acute hypersensitivity reaction occurs during ORBACTIV® infusion, discontinue ORBACTIV® immediately and institute appropriate supportive care. Before using ORBACTIV®, inquire carefully about previous hypersensitivity reactions to glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during ORBACTIV® infusion in patients with a history of glycopeptide allergy. In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV®-treated patients was 1.2 days and the median duration of these reactions was 2.4 days [see Adverse Reactions (6.1)].

5.3. Infusion Related Reactions

ORBACTIV® is administered via intravenous infusion, using a total infusion time of 3 hours to minimize the risk of infusion-related reactions. Infusion related reactions have been reported with the glycopeptide class of antimicrobial agents, including ORBACTIV®, that resemble “Redman Syndrome”, including flushing of the upper body, urticaria, pruritus and/or rash. Stopping or slowing the infusion may result in cessation of these reactions [see Adverse Reactions (6.1)].

5.4 Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs, including ORBACTIV®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

5.5 Potential Risk of Bleeding with Concomitant Use of Warfarin

ORBACTIV® has been shown to artificially prolong prothrombin time (PT) and international normalized ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an ORBACTIV® dose [see Warnings and Precautions (5.1)]. Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin [see Drug Interactions (7.9)].

5.6 Osteomyelitis

In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the ORBACTIV®-treated arm than in the vancomycin-treated arm. Monitor patients for signs and symptoms of osteomyelitis. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy [see Adverse Reactions (6.1)].

5.7 Development of Drug Resistant Bacteria

Prescribing ORBACTIV® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Patient Counseling Information (17)].

6. ADVERSE REACTIONS

The following adverse reactions are also discussed in the Warnings and Precautions section of labeling:

- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]
- Infusion Related Reactions [see Warnings and Precautions (5.3)]
- Clostridium difficile-associated Diarrhea [see Warnings and Precautions (5.4)]
- Osteomyelitis [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ORBACTIV® cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ORBACTIV® has been evaluated in two, double-blind, controlled ABSSSI clinical trials, which included 976 adult patients treated with a single 1200 mg intravenous dose of ORBACTIV® and 983 patients treated with intravenous vancomycin for 7 to 10 days. The median age of patients treated with ORBACTIV® was 45.6 years, ranging between 18 and 89 years of age with 8.8% ≥65 years of age. Patients treated with ORBACTIV® were predominately male (65.4%), 64.4% were Caucasian, 5.8% were African American, and 28.1% were Asian. Safety was evaluated for up to 60 days after dosing. In the pooled ABSSSI clinical trials, serious adverse reactions were reported in 57/976 (5.8%) patients treated with ORBACTIV® and 58/983 (5.9%) treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in ORBACTIV® and 12/983 (1.2%) in the vancomycin arm, respectively.

The most commonly reported adverse reactions (≥3%) in patients receiving a single 1200 mg dose of ORBACTIV® in the pooled ABSSSI clinical trials were: headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea. In the pooled ABSSSI clinical trials, ORBACTIV® was discontinued due to adverse reactions in 36/976 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 0.3%).

Table 1 provides selected adverse reactions occurring in ≥1.5% of patients receiving ORBACTIV® in the pooled ABSSSI clinical trials.

### Table 1: Incidence of Selected Adverse Reactions Occurring in ≥1.5% of Patients Receiving ORBACTIV® in the Pooled ABSSSI Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ORBACTIV N=976 (%)</th>
<th>Vancomycin N=983 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (3.7)</td>
<td>32 (3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>97 (9.9)</td>
<td>103 (10.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (4.6)</td>
<td>46 (4.7)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>26 (2.7)</td>
<td>26 (2.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>69 (7.1)</td>
<td>66 (6.7)</td>
</tr>
<tr>
<td><strong>General disorders and administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion site phlebitis</td>
<td>24 (2.5)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>19 (1.9)</td>
<td>34 (3.5)</td>
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<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
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<tr>
<td>Abscess (limb and subcutaneous)</td>
<td>37 (3.8)</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
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<tr>
<td>Alanine aminotransferase increased</td>
<td>27 (2.8)</td>
<td>15 (1.5)</td>
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<tr>
<td>Aspartate aminotransferase increased</td>
<td>18 (1.8)</td>
<td>15 (1.5)</td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
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</tr>
<tr>
<td>Tachycardia</td>
<td>24 (2.5)</td>
<td>11 (1.1)</td>
</tr>
</tbody>
</table>
6.1 Clinical Trials Experience (continued)
The following selected adverse reactions were reported in ORBACTIV®-treated patients at a rate of less than 15%:

• Blood and lymphatic system disorders: anemia, eosinophilia
• General Disorders and administration site conditions: infusion site erythema, extravasation, induration, pruritis, rash, edema peripheral
• Immune system disorders: hypersensitivity
• Infections and infestations: osteomyelitis
• Investigations: total bilirubin increased, hyperuricemia
• Metabolism and nutrition disorders: hypoglycemia
• Musculoskeletal and connective tissue disorders: tenosynovitis, myalgia
• Respiratory, thoracic and mediastinal disorders: bronchospasm, wheezing
• Skin and Subcutaneous Tissue Disorders: urticaria, angioedema, erythema multiforme, pruritis, leucocytoclastic vasculitis, rash.

7. DRUG INTERACTIONS
7.1 Effect of ORBACTIV® on CYP Substrates
A screening drug-drug interactions study indicated that ORBACTIV® is a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms [see Clinical Pharmacology (12.3)]. A drug-drug interaction study that assessed the interaction potential of a single 1200 mg dose of ORBACTIV® on the pharmacokinetics of S-warfarin (CYP2C9 probe substrate) showed no effect of ORBACTIV® on S-warfarin Cmax or AUC.

Avoid administering ORBACTIV® concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes, as co-administration may increase or decrease concentrations of the narrow therapeutic range drug. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given ORBACTIV® while on a potentially affected compound (e.g. patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin).

7.2 Drug-Laboratory Test Interactions
ORBACTIV® may artificially prolong certain laboratory coagulation tests (see Table 2) by binding to and preventing the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests [see Contraindications (4.1) and Warnings and Precautions (5.1, 5.5)]. For patients who require monitoring of anticoagulation effect within the indicated time after ORBACTIV® dosing, a non phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered.

ORBACTIV® does not interfere with coagulation in vivo. In addition, ORBACTIV® does not affect tests that are used for diagnosis of Heparin Induced Thrombocytopenia (HIT).

Table 2: Coagulation Tests Affected and Unaffected by ORBACTIV®

<table>
<thead>
<tr>
<th>Elevated by ORBACTIV®</th>
<th>Unaffected by ORBACTIV®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (PT) up to 12 hours</td>
<td>Chromogenic Factor Xa Assay</td>
</tr>
<tr>
<td>International normalized ratio (INR) up to 12 hours</td>
<td>Thrombin Time (TT)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT) up to 120 hours</td>
<td></td>
</tr>
<tr>
<td>Activated clotting time (ACT) up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Silica clot time (SCT) up to 18 hours</td>
<td></td>
</tr>
<tr>
<td>Dilute Russell’s viper venom time (DRVT) up to 72 hours</td>
<td></td>
</tr>
<tr>
<td>D-dimer up to 72 hours</td>
<td></td>
</tr>
</tbody>
</table>

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C
Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oritavancin at the highest concentrations administered, 30 mg/kg/day and 15 mg/kg/day, respectively. Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies.

There are no adequate and well-controlled trials in pregnant women. ORBACTIV® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is unknown whether oritavancin is excreted in human milk. Following a single intravenous infusion in lactating rats, radio-labeled [14C]-oritavancin was excreted in milk and absorbed by nursing pups. Caution should be exercised when ORBACTIV® is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of ORBACTIV® in pediatric patients (younger than 18 years of age) has not been studied.

8.5 Geriatric Use
The pooled Phase 3 ABSSSI clinical trials of ORBACTIV® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate renal impairment [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]. The pharmacokinetics of ORBACTIV® in severe renal impairment have not been evaluated. ORBACTIV® is not removed from blood by hemodialysis.

8.7 Hepatic Impairment
No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of ORBACTIV® in patients with severe hepatic insufficiency has not been studied [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

10. OVERDOSE
In the ORBACTIV® clinical program there was no incidence of accidental overdose of ORBACTIV®.

Based on an in vitro hemodialysis study, ORBACTIV® is unlikely to be removed from blood by hemodialysis. In the event of overdose, supportive measures should be taken.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals have not been conducted to determine the carcinogenic potential of oritavancin. No mutagenic or clastogenic potential of oritavancin was found in a battery of tests, including an Ames assay, in vitro chromosome aberration assay in Chinese hamster ovary cells, in vitro forward mutation assay in mouse lymphoma cells and an in vivo mouse micronucleus assay.

Oritavancin did not affect the fertility or reproductive performance of male and female rats exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). Those daily doses would be equivalent to a human dose of 300 mg, or 25% of clinical dose. Higher doses were not evaluated in nonclinical fertility studies.
Dual Therapy MK-8591 Plus Doravirine Is Efficacious in Treatment-Naïve PLWH

BY CONTAGION® EDITORIAL STAFF

A new class of treatments known as nucleoside reverse transcriptase translocation inhibitors (NRTTs) is showing promise in helping treatment-naïve people living with HIV (PLWH) achieve viral suppression. At the 10th International AIDS Society Conference on HIV Science (IAS 2019), investigators presented 48-week efficacy and safety data from a study evaluating MK-8591, the first drug in this new class, in combination with doravirine (DOR), a recently approved nonnucleoside reverse transcriptase inhibitor.

For the first 24 weeks, participants in the phase 2b, randomized, double-blind, comparator-controlled, dose-ranging trial received 1 of 3 doses of MK-8591 (0.25, 0.75, or 2.25 mg) plus DOR (100 mg) and lamivudine (3TC [300 mg]) or DOR/3TC/tenofovir disoproxil fumarate (TDF) once daily with placebo.

Participants taking MK-8591 who achieved HIV-1 RNA <50 copies/mL were switched to a 2-drug regimen of MK-8591 and DOR after 24 weeks, with the primary efficacy end point comprising the overall proportion of participants at week 48 with HIV-1 RNA <50 copies/mL using the US Food and Drug Administration snapshot approach.

Investigators defined virologic failure as rebound with confirmed HIV-1 RNA ≥50 copies/mL after suppression or nonresponse with confirmed HIV-1 RNA ≥50 copies/mL by week 48.

A total of 121 participants (mean age of 31 years, 92.6% male, 76.0% white, 22.0% HIV-1 RNA >100,000 copies/mL) were included in the study. The percentage of participants who achieved HIV-1 RNA <50 copies/mL in the 0.25-, 0.75-, and 2.25-mg MK-8591 dose groups was 89.7% (26 of 29), 90.0% (27 of 30), and 77.4% (24 of 31), respectively, at week 48. A total of 83.9% (26 of 31) of participants achieved it with DOR/3TC/TDF.

By week 48, 6 participants had met the definition of protocol-defined virologic failure: 5 of 90 (5.6%) in the MK-8591 groups (4 rebound, 1 nonresponse) and 1 of 31 (3.2%) in the DOR/3TC/TDF group (rebound); none had HIV-1 RNA >200 copies/mL or documented resistance to study drugs.

From baseline through week 48, the mean change in CD4-positive T-cell count was similar across all groups, and the proportion of participants on the 2-drug regimen for 24 weeks with HIV-1 RNA <50 copies/mL was similar across doses (88.9%-90.0%).

Drug-related adverse events (AEs) were reported by 19.4% of DOR/3TC/TDF participants compared with 7.8% of MK-8591 participants (in any dose group), although none of the MK-8591 AEs were considered serious.

“Similar proportion of participants achieved and maintained viral suppression at week 48 across all treatment groups. MK-8591+DOR was well-tolerated regardless of dose,” investigators concluded.

The study, MK-8591 at Doses of 0.25 to 2.25 mg QD, in Combination With Doravirine Establishes and Maintains Viral Suppression Through 48 Weeks in Treatment-Naïve Adults With HIV-1 Infection, was presented on Wednesday, July 24, 2019, at IAS 2019 in Mexico City, Mexico. ▲

HOPE: Dapivirine Vaginal Ring Is a Promising HIV Prevention Modality

BY CONTAGION® EDITORIAL STAFF

In 2016, the ASPIRE trial demonstrated that a monthly vaginal ring containing dapivirine 25 mg used regularly could safely and effectively reduce a woman’s risk of acquiring HIV-1 infection by up to 56%.

Now, final results of HOPE, a phase 3 open-label extension trial, show high uptake and lower-than-anticipated HIV-1 incidence among women in southern and eastern Africa who used the ring continuously for 4 weeks and then swapped it out for a new one. The findings were presented on Tuesday, July 23, 2019, at IAS 2019 in Mexico City, Mexico.

HOPE, the HOPE Extension Trial of the Dapivirine Vaginal Ring, was presented on Wednesday, July 24, 2019, at IAS 2019. ▲

A total of 1342 (92%) women accepted the dapivirine ring at baseline, with 90%, 98%, 87%, 83%, and 79% acceptance at months 1, 2, 3, 6, and 9, respectively, and 86% of returned rings displayed residual dapivirine levels consistent with some use in the prior month (>0.9 mg released).

Thirty-five HIV infections were observed (incidence, 2.7 per 100 person-years; 95% CI, 1.9-3.8), a statistic that fell below the expected incidence rate of 4.4 per 100 person-years (95% CI, 3.2-5.8) in the absence of access to a dapivirine vaginal ring.

According to investigators, incidence of ≥2.7 would be expected to occur in fewer than 33 in 10,000 samplings (0.33%).

HIV prevention modalities that do not involve a daily pill burden are needed in places where individuals may not have easy access to health care. The HOPE results support the dapivirine vaginal ring as a potential option.

The study, High Adherence and Sustained Impact on HIV-1 Incidence: Final Results of an Open-Label Extension Trial of the Dapivirine Vaginal Ring, was presented on Tuesday, July 23, 2019, at IAS 2019 in Mexico City, Mexico. ▲
Ticks are dangerous vectors that can transmit deadly diseases to humans and animals alike. As such, developing effective methods to prevent the spread of tickborne diseases is of paramount concern.

A team of investigators from the Department of Entomology at Louisiana State University previously recognized that the salivary gland of a tick is critical to sustaining life and therefore may be a potential target tissue for acaricides.

The team hypothesized that the functioning of the tick’s salivary gland relies on the epithelial transport of potassium ions and that the chemical modulation of inward rectifier potassium (Kir) conductance would have an effect on the biology of ticks. The findings of their research were presented at the American Chemical Society (ACS) Fall 2019 National Meeting & Exposition.

For the study, the research team fed ticks blood laced with 2 compounds documented to act on the Kir channels. According to the investigation, 2 of the molecules, VU0071063 and pinacidil, were effective and reduced saliva secretion by ≥95% and reduced blood ingestion approximately 15-fold. Furthermore, ticks that fed on blood infused with either of these compounds died within 12 hours of ingestion. This is significant because transmission of pathogens through a tick bite takes a minimum of 12 hours.

The team also noted that ticks that were removed from the blood meal prior to death were lethargic and unable to walk, which may be attributable to an imbalance of potassium, sodium, and chloride ions. Typically, ticks return excess waters and ions back into the host when feeding, but in this situation, the ticks produced more ions despite less saliva production. The investigators hypothesized that an effect on the nervous system led to disruption of the biological function.

Because the investigators conducted this research in artificial host feeding systems with blood meal, the next step is to evaluate this method when ticks feed on rodents.

According to the press release issued by ACS, the study team hopes that in the future, these findings can be used to develop a spray, injection, or other treatment to reduce the risk of tick bites in animals.

“These data strongly suggest Kir channels are critical for salivary gland function of ticks and are promising target sites for the development of novel acaricides,” the investigators wrote in the abstract.

The study, Giving Ticks ‘Dry Mouth’ Through Chemical Modulation of Inward Rectifier Potassium Channels as a Mechanism to Prevent Blood Feeding, was presented on August 26, 2019, at ACS Fall 2019 in San Diego, California.

A new portable, smartphone-based detection system developed by investigators at the University of Arizona uses a fluorescence microscope assay to identify a minuscule amount of norovirus particles in water samples. Because norovirus is highly contagious in low concentrations, detection is typically conducted via a polymerase chain reaction–based method. But that requires time, a lab setting, and trained personnel.

“It only takes a very small number of norovirus particles to cause an infection in humans, so we need a really sensitive detection method,” Jeong-Yeol Yoon, PhD, professor of biomedical engineering at the University of Arizona, who led the team, said in a press release. “Also, scientists aren’t able to culture norovirus in the lab, and available antibodies to the pathogen aren’t very strong.”

In findings presented at the American Chemical Society (ACS) Fall 2019 National Meeting & Exposition, the research team unveiled their smartphone-based device, which features a fluorescent microscope made from a commercially available light microscope accessory, a separate light source, and 2 band-pass filters. The system also has a paper microfluidic chip, to which a water sample containing norovirus is added and then mixed with a suspension of fluorescent beads with norovirus antibodies attached. The beads bind to the virus particles and gather in larger, more identifiable fluorescent groups.

Investigators photographed the chip with the smartphone fluorescent microscope and ran the images through a companion app to calculate norovirus concentrations. As few as 10 norovirus particles are enough to sicken an individual.

“The lowest detection limit corresponded to about 5 or 6 norovirus particles per sample, so it’s very close to the single-virus level,” Yoon said in the press release. “When norovirus reaches levels detectable by other methods, the person is already seriously ill. But if we can detect the virus earlier, they can receive medical care sooner.”

Yoon and his team recently created a 3-D-printed case to house the whole device and make it more portable. The only remaining issue involves the water source for testing. The device proved effective at detecting norovirus in both purified and reclaimed wastewater samples, but the team hit a snafu in testing tap water.

“We believe that the chlorine in tap water is affecting the assay,” Yoon said. “We don’t think it will be a problem to treat the water to remove chlorine before performing our method.”

The study, Smartphone-Based Paper Microfluidic Particulometry of Norovirus From Environmental Water Samples at Single Copy Level, was presented on August 27, 2019, at ACS Fall 2019 in San Diego, California.

Norovirus Detection Goes Mobile With Smartphone-Based Device

BY ALEXANDRA WARD, MA

ACS FALL 2019 MEETING & EXPOSITION

Disruption to Balance of Ions in Salivary Glands of Ticks May Limit Pathogen Transmission

BY MICHAELA FLEMING
CASE STUDY

Eosinophils, Fevers, and Diarrhea With a Surprise Diagnosis in a Patient With AIDS

When the CD4 count seems too good to be true.

BY GREG WHITEHILL, TEMITAYO ADEGOKE; AND NNAEMEKA ONYEKABA, MD

FINAL DIAGNOSIS
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

HISTORY OF PRESENT ILLNESS
A 31-year-old male patient with AIDS (last CD4 count, 77; 3 weeks prior) presented to clinic with a 3-day history of abrupt-onset fatigue, abdominal pain, high-output diarrhea, nausea, weakness, nasal congestion, and dry cough. His stools were watery, nonbloody, and green in color, with a frequency of 5 to 10 episodes daily. He also described progressive, diffuse pruritus over the prior 2 weeks.

Of note, the patient carried a diagnosis of HIV and, in the years leading to presentation, was antiretroviral nonadherent. Six months prior to admission, he was started on antiretroviral therapy and achieved regression of viral load from 269,000 to undetectable within 4 months, with an increase in CD4 count to 77 from 34. Two weeks later, he developed herpes zoster in unilateral trigeminal V2 distribution with overlying impetigo, thought to be a manifestation of immune reconstitution inflammatory syndrome (IRIS). He subsequently developed debilitating postherpetic trigeminal neuralgia and was treated with carbamazepine and gabapentin. The patient was adherent with antiretroviral therapy and appropriate opportunistic infection prophylaxis throughout this time.

The patient was sent to the emergency department for inpatient work-up of diarrhea. Initial differential was broad given the patient’s AIDS status, with high suspicion for viral, bacterial, or parasitic gastroenteritis.

PHYSICAL EXAMINATION
Physical examination at presentation was unremarkable aside from mild tachycardia of 105 beats per minute and diffuse abdominal tenderness without guarding. He was afebrile with nonlabored respirations. Oropharynx was clear, lungs were clear to auscultation, extremities were nonedematous, and no lymphadenopathy was appreciated. Despite the patient’s pruritus, skin examination revealed only mild excoriations on the arms and trunk, with no rashes.

STUDIES
On admission, the patient’s labs showed a nonanion gap metabolic acidosis with respiratory compensation, consistent with lower gastrointestinal fluid loss in the setting of diarrhea. Metabolic panel also revealed creatinine level elevation to 3 times the baseline, with a ratio of blood urea nitrogen to creatinine of 9. Urinalysis revealed proteinuria and granular casts; urine cultures were negative. Complete blood count demonstrated a neutrophilic predominant leukocytosis with left shift. Absolute eosinophil count was elevated, at 6000 cells/µL. CD4 T-cell count was 748, up from 77 three weeks prior. The normal CD4 count was regarded with suspicion given the recent AIDS status, and initial diarrhea work-up included opportunistic infections with high suspicion for parasites. Stool specimen showed many white blood cells. Work-up was negative for stool ova/parasites, Microsporidium, Cryptosporidium, Isospora, Clostridioides difficile, acid-fast bacilli (AFB) smear, giardia, and shiga toxin. Strongyloides serology; hepatitis A, B, and C serology; histoplasma urine antigen; Aspergillus antigen; and (1,3)-β-D-glucan were negative as well. No AFB grew in blood cultures. Abdominal computed tomography (CT) was significant for only diffuse lymphadenopathy.

NEW PATIENT

greg whitehill

Whitehill is a fourth-year medical student at Drexel University College of Medicine currently applying for residency in internal medicine. He has a long-standing interest in hematology/oncology and has recently developed a waxing fascination with infectious disease.

Temitayo Adegoke

Adegoke is a fourth-year medical student from Long Island, New York, pursuing a career in internal medicine. She is passionate about patient advocacy and delivering high-quality care to underserved communities.

nnaemeka onyekeba, md

Onyekeba is a second-year infectious disease fellow at Cooper University Hospital in Camden, New Jersey.
Pertinent positive results included remarkably elevated serum immunoglobulin (Ig) E at 48,647 units/mL, bronchial wash positive for adenovirus serogroup C, positive human herpesvirus 6 (HHV6), and Epstein-Barr virus (EBV) in blood.

**DIAGNOSTIC PROCEDURES AND RESULTS**

Upper and lower enteroscopy showed normal stomach and duodenum, diffuse colitis, and nodularity of the terminal ileum. Biopsy showed moderate duodenitis, moderate ileitis, and severe crypt destructive colitis, with pathologic findings suggestive of chronic enteric infection. Granulomas, Cryptosporidium, AFB, and cytomegalovirus (CMV) were absent.

**CLINICAL COURSE**

After receiving 2 days of fluids and broad-spectrum antibiotics, the patient left against medical advice, only to return the next day with persisting symptoms. Shortly after readmission, the patient developed tachycardia and tachypnea, which progressed over 3 days to respiratory failure requiring transfer to the intensive care unit (ICU) and intubation on hospital day 8. Immediately before initial intubation, the patient’s exam was significant for a respiratory rate greater than 40 breaths per minute, diffuse reitations, and absent breath sounds. Along with respiratory failure, the patient also developed worsening fevers, leukocytosis, thrombocytopenia, transaminitis, and hypereosinophilia, along with facial and extremity edema on exam (see **FIGURE** online). HHV6 was positive in blood, and respiratory virus panel was positive for adenovirus.

After intubation, the patient was started on a 9-day methylprednisolone taper for suspected DRESS and experienced gradual symptomatic improvement and resolution of hyper eosinophilia (see **Figure** online). Treatment of adenovirus was considered but decided against because of acute liver injury. On hospital day 17, the patient was considered but decided against because of acute liver injury. On hospital day 17, the patient was hospitalized for 2 months, with 1 month spent in the ICU. He was ultimately discharged to a rehabilitation facility with tracheostomy and gastrostomy tube in place to begin recovery after a lengthy hospital course.

**DISCUSSION**

DRESS is a moderate-to-severe reaction with onset generally occurring 2 to 6 weeks after drug initiation. DRESS encompasses a diverse yet distinct set of reactions characterized by fevers, rash, leukocyte abnormalities, and multigland syndromes. The RegiSCAR and JSCAR criteria have been proposed for diagnosis of DRESS. RegiSCAR criteria describe potential DRESS if the reaction was suspected to be drug related and the patient required hospitalization with 3 or more of the following findings: acute skin rash, fever, lymphadenopathy, visceral organ involvement, leukocytosis, eosinophilia, thrombocytopenia. The JSCAR criteria are similar but notably include prolonged symptoms longer than 2 weeks following drug discontinuation and HHV6 reactivation. Mortality is estimated at 10% and is usually due to hepatic necrosis. Carbamazepine is the agent most commonly implicated in DRESS. Risk for developing DRESS is multifactorial, but the reaction appears to emerge within a milieu of drug toxicity and maladaptive immune response. Mutations in drug detoxification and metabolism enzymes, which result in accumulation of toxic metabolites, have been implicated in anticonvulsant- and sulfonamide-associated DRESS. Certain HLA haplotypes are associated with increased risk, with reactions to carbamazepine being associated with HLA-A*3101, A*11, and B*51. These associations, along with a 2- to 6-week delay in symptom onset after drug initiation, suggest a delayed-type, hypersensitivity-like reaction to the drug, immunogenic metabolites, or haptens. Indeed, T cells reacting to carbamazepine have been identified in patients. However, other immunologic and infectious phenomena observed in DRESS suggest a more complex pathogenesis. In initial stages of disease, patients enter an immunosuppressive state characterized by increased regulatory T cells and decreased IgG and IgA. Within this environment, latent herpesviruses sequentially reactivate, either by direct stimulation from the drug or by virtue of opportunity. HHV6 reactivation, generally measured as a rise in HHV6 IgG, is especially characteristic. Generally HHV6 and EBV are seen early in disease, and CMV is seen as the patient experiences sequential flares. As disease progresses, an expansion of cytotoxic T lymphocytes occurs, heralding systemic inflammation. Activity of cytotoxic T cells against tissues harboring reactivated virus is thought to be a significant cause of organ damage.

Vesicular organ involvement is the major cause of morbidity in DRESS syndrome. The most frequently involved organs, in order, are the liver, the kidney, and the lung. Gastrointestinal involvement is rare but can be serious and often leads to dehydration. Cases of DRESS involving noninfectious, inflammatory colitis have been described in reactions to carbamazepine and vancomycin. Skin involvement is reported in up to 100% of DRESS reactions. Maculopapular rash is most common, but cutaneous manifestations are highly variable and range from erythema to toxic epidermal necrolysis. Facial edema is common, as well, present in up to 76% of cases. Cases of DRESS without rash have been reported, but they are rare.

This patient is somewhat of an atypical case, presenting with diarrhea. No rash was observed throughout the hospital course, with the only cutaneous findings being pruritus and facial edema. The patient did, however, qualify for RegiSCAR criteria, with development of fevers, hyper eosinophilia, lymphadenopathy, and organ involvement—namely liver, lung, and potentially kidney. With persistence of symptoms and a finding of HHV6, the patient also qualified as an atypical case of DRESS per JSCAR criteria.

Treatment of DRESS begins with immediate withdrawal of the offending drug. Improvement of symptoms and lab abnormalities is best achieved with corticosteroids and supportive care.

Intravenous Ig treatment has been proposed but carries a high risk of severe adverse effects and is thus advised against. As viral reactivation plays an integral role in disease pathogenesis, antivirals such as ganciclovir and cidofovir have been used, as well, but toxicity is a major concern in the setting of multigland disease. Cidofovir is the only agent with consistent demonstrable efficacy against adenovirus. Cidofovir treatment was considered in the patient after evidence of adenovirus in bronchoalveolar lavage was found, but the risk of nephrotoxicity was considered too great.

Corticosteroids, though efficacious, may increase the risk of developing infection and even sepsis by exacerbating the patient’s already immunosuppressed state.

Patients with AIDS present a unique challenge in both diagnosis and treatment of DRESS. The multigland manifestations of DRESS, when presenting in patients with AIDS, require extensive work-up to rule out a readily treatable infectious cause. As mentioned, corticosteroids are the only known effective treatment for DRESS but may increase risk of secondary infection or exacerbate existing infection. Furthermore, DRESS in itself is associated with an immunosuppressive state in which reactivation of latent viruses leads to morbidity and organ damage through intense inflammatory response. Descamps et al have noted that DRESS-like syndromes occur in immunosuppressed patients in the absence of an offending drug, which they have proposed may represent a “viral reactivation with eosinophilia and systemic symptoms.” One such example is IRIS, which in this patient manifested with an immune response to the zoster herpesvirus. This overlap in disease mechanism can complicate the distinction between DRESS and IRIS, especially as many drugs frequently used in patients with AIDS have been implicated in DRESS, including antibiotics such as trimethoprim/sulfamethoxazole, mycobacterial therapies, and antiretrovirals such as raltegravir and dolutegravir. Cases of DRESS in patients with AIDS are rarely shared in the literature, perhaps because of low incidence. Practitioners who observe this syndrome in immunocompromised individuals and patients with AIDS should share their experience to better elucidate how clinicians can optimize DRESS therapy for this vulnerable population.

References available at ContagionLive.com.
The healthcare industry is evolving at a rapid pace. The need for relevant expert-driven opinions and insights is crucial to continuing the advancement of patient outcomes. With platforms like HealthAdviser, physicians and healthcare professionals can empower their voice to make a difference in market research studies designed to have an impact on the pharmaceutical and healthcare industries. HealthAdviser is a community of nearly 20,000 healthcare professionals who are given an opportunity to participate in market research studies from HRA®, a trusted market research firm for over 40 years, and earn honoraria for their contributions.

“It empowers subject-experts by providing them with a platform to share knowledge unique to their experience as a HCP, patient, or caregiver”, said Ryan Pitcherello, Quantitative Operations Associate at HRA. “This gives them the opportunity to make a difference on a larger scale than would be possible in their day-to-day duties,” said Pitcherello.

Aside from earning honoraria, healthcare professionals can make a difference with an opportunity to shift the industry with their opinions and to further their relationships with their peers. “The importance of registering for the HealthAdviser panel is that it allows you as a customer or stakeholder the ability to participate in research studies, by providing your opinions. These opinions help others understand the needs for, new products and/or improvements on existing products,” said Patrick Chapman, Senior Manager, Qualitative Field Operations and Conference Controller at HRA. “Your participation in market research helps with decisions on goods and services and why customers may choose a brand or service over a competitor. Market research identifies new business opportunities and the change of market trends,” said Chapman.

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