

Better Options Available For Multidrug-Resistant HIV

By Karen Blum

Patients with multidrug-resistant HIV currently make up a smaller but still challenging part of the population living with HIV. With careful monitoring and new drugs coming, providers can still help their patients.

“It’s really great that we have a relatively low number of patients with this issue,” said Milena Murray, PharmD, MSc, BCIDP, AAHIVP, an associate professor of pharmacy practice at Midwestern University-Chicago College of Pharmacy, and an HIV/ID clinical pharmacist at Northwestern Memorial Hospital, in Chicago. “Patients can have one or two mutations and still have plenty of options at this point.”

About 3% to 7% of the HIV population are considered multidrug-resistant (MDR) and need additional new agents, according to Michael Kozal, MD, a professor of medicine at the Yale School of Medicine in New Haven, Conn., and the chief of staff at the VA Connecticut Healthcare System. He has studied HIV multidrug resistance since 1991.

People can develop resistance to multiple drugs for several reasons, experts said.



Children who acquire HIV perinatally often have problems adhering to medication, and can burn through several drugs by the time they reach adolescence and young adulthood. Some patients are less adherent to medication because they’re in and out of the criminal justice system, have substance use issues or for other reasons, and develop viral mutations that

render the drugs ineffective. Additionally, some patients experience toxicities or cannot tolerate some of the existing drug classes, or are long-term survivors initially diagnosed in the late 1980s to early 1990s who have gone through a myriad of drugs over time.

“We have had a number of great agents over six different drug classes, but some people develop drug resistance,” Kozal said. “It sounds like a lot—six classes—but as patients have reactions, it limits the drugs they can take, and some patients are infected with drug-resistant virus. There is a need for new agents that have different mechanisms of action.”

Until the past couple of years, there were a limited number of targets on the human immunodeficiency virus that could be hit by available medications, said Jonathan Appelbaum, MD, FACP, AAHIVS, a professor and the chair of the Department of Clinical Sciences at Florida State University College of Medicine, in Tallahassee

Recently, several new targets have emerged, including drugs designed to inhibit the maturation of the virus inside cells or prevent its entry into immune system T cells.

“The good thing about these new drugs is they don’t show cross-resistance to the existing drugs, because their mechanisms of action are different,” Appelbaum said. “If you’re resistant to the older drugs, you are not automatically resistant to these.”

New Medication Help

One of the newer medications is an attachment inhibitor, ibalizumab-uiyk (Trogarzo, Theratechnologies), approved by the FDA in 2018. The drug has a novel mechanism of action. A monoclonal antibody that binds to the surface of immune cells, ibalizumab blocks the steps required for viral entry into cells. Multiple centers participated in the pivotal study the FDA considered for approval, enrolling 40 patients with MDR HIV. Patients received a dose of IV ibalizumab-uiyk in addition to their failing regimen for one week. After that period, they received ibalizumab-uiyk with optimized treatment regimens for six months. After one week on ibalizumab-uiyk, most patients (83%) experienced a decrease in viral load (*N Engl J Med* (<https://www.nejm.org/doi/full/10.1056/NEJMoa1711460>) 2018;379[7]:645-654). After 25 weeks, nearly half saw their viral load fall below the level of detection. The researchers also reported an increase in CD4 T cells, which are a marker of immunity.



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Source: *N Engl J Med* 2018;379[7]:645-654

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“This is a great drug that has worked well,” Appelbaum noted, but because it is given intravenously, it’s not used early in HIV treatment.

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The FDA recently approved fostemsavir (Rukobia, ViiV Healthcare), which was developed specifically for patients with MDR HIV and works by a novel mechanism of action, said Kozal, the lead author on a recent article (*N Engl J Med* (<https://www.nejm.org/doi/full/10.1056/NEJMoa1902493>) 2020;382:1232-1243) describing phase 3 trial results.

Fostemsavir is a prodrug whose active metabolite, temsavir, is an attachment inhibitor that prevents viral entry into host immune cells by binding to a glycoprotein on the surface of the virus. In the ongoing BRIGHTE trial in 23 countries, 371 patients with MDR HIV-1 infection were given fostemsavir along with their failing HIV regimen. After 48 weeks of therapy, 54% of randomized and 38% of nonrandomized patients who took the drug had undetectable viral RNA levels. The most common side effects included diarrhea, nausea and upper respiratory tract infections.

“The data were very promising in that the viral load stayed nondetectable in a large number of patients out to week 48,” Kozal said. “There’s no cross-resistance to other classes, so we think it’s going to be helpful for people who have exhausted other drug classes or can’t take other drug classes because [of intolerance].”

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Current management of patients still comes down to individual resistance profiles, Murray said. Protease inhibitors are good options for some patients with drug resistance.

Maraviroc can be helpful but requires a tropism assay. Enfuvirtide (Fuzeon, Genentech) is an injectable that may cause painful injection site reactions and is usually used as a last resort. At times, adding an integrase inhibitor to the regimen will be enough if there are no mutations to this class.

“Sometimes we need to have patients on four to five medications, but that regimen is able to get them to an undetectable viral load,” Murray said, while other times medications are not enough to get to undetectable but can keep the viral load at a lower point. Ibalizumab can be a good option for patients who are extensively drug-resistant, she added.

“One of the caveats of HIV treatment is you never want to add on or substitute just one drug if patients have resistance to multiple drugs,” Appelbaum noted. “You want to have two, and ideally three, active medications.”

When monitoring patients, Murray said, always check the viral load. “If patients are undetectable, that’s the best case scenario,” she said. “But if we can’t get them to undetectable, we want to make sure their viral load isn’t continuing to increase.”

Don’t Forget CD4 Counts

In addition, monitor CD4 counts to make sure they’re not decreasing. Check for any signs or symptoms of opportunistic infections and make sure any comorbid conditions are being addressed. Follow all guideline recommendations for screenings.

T-cell count also is important, Appelbaum said, “because if you don’t have the virus under control, the immune system is being constantly attacked by the virus, and so the patient is at risk for opportunistic infections and malignancies.”

Be mindful that as patients get older and need to add statins or antihypertensives to their regimens, drug interactions can occur with their HIV medications, Murray said. Then you can run into the issue of not being able to change the antiretroviral therapy to mitigate drug interactions because there aren’t any other options to treat the drug-resistant HIV.

Overall, have good encouragement and support for your patients, Kozal advised: “You’ve got to take the drugs in order for them to work.”

Appelbaum reported a relationship with Merck and ViiV Healthcare. Murray reported a relationship with Merck.