FDA approves treatment for multi-drug resistant HIV

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Lenacapavir, an injection, has been approved by the FDA for multi-drug resistant HIV.

HIV is not curable yet, but it can be treated successfully throughout someone's lifespan. "And so, in the field, we want to ensure that the treatments we have—which for now are for a lifetime—become easier, simpler to use, and safer, and remain highly effective for our patients," said Onyema Ogbuagu, MD, who is associate professor of medicine (AIDS) and director of the Yale Antivirals and Vaccines Research Program of the Yale HIV/AIDS Program in the Section of Infectious Diseases of Yale School of Medicine.

Through collective pursuit in the research world, a new class of HIV treatment was born: long-acting HIV medications that target the capsid of HIV-1, which is a conical structure that harbors its genome.

"Lenacapavir is one of those agents, and it is currently the longest-acting agent approved [by the Food and Drug Administration (FDA)] for HIV treatment," Ogbuagu said. Lenacapavir got FDA approval based on the data in Ogbuagu's study, which has now been published in *The Lancet HIV*.

Lenacapavir joined a new class of antiretroviral therapy (ART) that "had never existed before," Ogbuagu said.

Because of its novelty, the drug has a high chance of success since people have not been exposed to it before. It tackles one of the biggest issues when it comes to medication for treatment of HIV: drug resistance .

"We define [HIV multi-drug resistance] by people having resistance to two or more drugs in at least three of the four main classes of drugs, and who have fewer than two effective drugs left" to be used as treatment within each of the different classes, Ogbuagu explained.

Some people's viral infection develops resistance to HIV treatments over

time. Others have acquired HIV from people who already had developed resistance to multiple HIV medications.

"They are typically people who were on HIV treatments, and, either because they were put on the wrong medication, or they didn't take the medication as prescribed, they can develop resistance to HIV treatments. The people in the study had multi-drug resistance," Ogbuagu explained.

How lenacapavir is being studied

To conduct the third phase of the drug trial, Ogbuagu and colleagues treated three groups of patients with lenacapavir tablets, and with injections that went under the skin.

First, they measured how lenacapavir worked on its own to decrease the virus in the bodies of the people who participated in the trial.

There were three groups of individuals in the study. One was immediately switched off their failing treatments and placed on lenacapavir, along with at least one or more additional HIV drugs.

For the other two, the researchers randomly gave lenacapavir to one group and a placebo to the other in a 2:1 ratio for two weeks. Those who received lenacapavir tablets for the first two weeks took weekly doses. After the two weeks, they added new drugs to replace the current therapy the person was on that had not been effective.

Subsequently, they tested people to check the amount of viral copies they had in their bloodstream.

"We found that we had suppressed 88% of viral copies in the arm where people had received lenacapavir, and suppressed only 17% in people who received the placebo in the arm," Ogbuagu noted, "and then we

followed them out to a year."

Ogbuagu added that "for a group of patients with HIV who have very limited treatment options, due to drug resistance, or intolerance, or safety concerns," the drug managed to suppress the virus in over 80% of individuals. "That's incredible," he said.

The clinical trials were done with a relatively small group of people since only 8% or less of all the HIV patient population has multi-drug resistance and met that definition in the study, said Ogbuagu. Still, the study's enrollment numbers were sufficient for the FDA since only a small number of people could meet the criteria of the study.

When the study, which was done with FDA oversight, met research goals, the agency approved 927 milligrams of lenacapavir injections, separated into two doses, to be received twice per year. Lenacapavir tablets of 300 milligrams were approved for use only as a loading dose—for an initial lead-in option before switching to the injection in the study.

In addition, Ogbuagu and his team decided to use lenacapavir tablets in the trial so that people would not skip any doses if they were going to miss an injection appointment during the peak of the pandemic of COVID-19. "So, we gave people tablets to take once weekly as a bridge," he said. This form of the therapy is not yet approved by the FDA and thus not available to the public.

Data at the end of the first year of their trial showed that receiving the injection helped people strengthen their immune system. Ogbuagu expects this will likely to translate to better protection against possible opportunistic infections like salmonella and tuberculosis, and also to lower the associated risk of death.

How this new HIV drug therapy works

In essence, lenacapavir tackles the capsid, a conical structure that harbors the RNA (ribonucleic acid) of HIV and other proteins that HIV uses to enter and replicate in human cells. The medication works in two ways: First, it interrupts viral replication by preventing HIV from reaching the nucleus of an infected cell, which then blocks reproduction.

The second mechanism is for cases in which integration of the HIV genome has already occurred. In this instance, lenacapavir interferes with production of viral progeny, "making them defective so that they are not able to infect other cells." Therefore, it works in both early and late stages of the HIV life cycle to disrupt replication.

Ogbuagu said that this medication—which tackles the HIV-1 strain—also appears to have a unique ability to prevent HIV-1. He and other investigators are now enrolling patients in other studies to further evaluate it for that purpose.

It is also a very potent medication so "a little goes a long way," said Ogbuagu. Patients would only need a lenacapavir injection every 26 weeks, which is approximately every six months.

Besides possible, and mostly minor, injection-site reactions, he added that the drug showed itself to be safe and was well-tolerated.

Ogbuagu also highlighted that the lenacapavir injection should be combined with one or two other HIV medications as treatment for people who live with HIV multi-drug resistance.

Simplifying treatment options for multi-drug resistant HIV

According to Ogbuagu, lenacapavir "opens the door to simplify treatments for people who previously had not had any good options."

The fact that patients must visit the clinic to receive the injection gives the provider more control, as they can be sure the drug is correctly administered and that all doses are given in a timely fashion. This is important for people who face obstacles to receive HIV treatment due to work schedules, housing insecurity, or "too many other social determinants of health challenges" they might have to face.

Ogbuagu added that it also reduces "the stigma associated with [taking] a daily pill."

"It has been a challenge in the field to have simple treatment for this type of patient," Ogbuagu concludes, "so the approval of lenacapavir is something we should be very proud of."

More information: Onyema Ogbuagu et al, Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial, *The Lancet HIV* (2023). DOI: 10.1016/S2352-3018(23)00113-3

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