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Researchers find drug-resistant HIV patients with unimpaired immune cells

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Mayo Clinic researchers have shown why, in a minority of HIV patients, immune function improves despite a lack of response to standard anti-retroviral treatment. In these cases, researchers say, the virus has lost its ability to kill immune cells. The findings appear in the online journal *PLoS Pathogens*.

The goal of current treatments for HIV is to block the virus from reproducing, thereby allowing the immune system to repair itself. These findings show for the first time that not all HIV viruses are equally bad for the immune system. Patients who harbor these viruses do not develop certain complications of the disease because of mutations that render some HIV drugs ineffective -- but also impair the ability of the virus to cause disease.

"These findings suggest -- in contrast to how these patients have been treated in the past -- that changing treatments might not be needed in order to help the immune system," says Andrew Badley, M.D., Mayo infectious disease researcher and senior author of the study.

HIV causes disease by progressively killing CD4 T cells, whose function is to orchestrate the immune system. Loss of these cells renders patients susceptible to unusual infections and cancers. Over time, HIV mutates and can become resistant to the drugs used for treatment. Mayo researchers have discovered that viruses with certain mutations that render a component of the drug cocktail used to treat HIV infection ineffective also have an impaired ability to kill CD4 T cells. Even though

mutated viruses replicate as well as normal HIV, they fail to cause the infected cells to die. Not all mutant viruses share this effect; only selected mutations cause the impairment in cell killing, without effecting virus replication.

HIV has evolved many ways to cause the death of CD4 T cells, most of which involve HIV accelerating the normal cell death. One kind of cell death that is unique to HIV involves the HIV enzyme protease, whose normal job is to cut up viral proteins so they can be used. This same process also cuts a normal cell protein which creates a novel protein called Casp8p41. This protein is only created during HIV infection. Casp8p41 in turn is responsible for the death of many of the infected cells. Researchers found that cells infected with HIV that also contain the mutations, produced less Casp8p41, and therefore fewer of the infected cells died.

The current treatment for HIV involves measuring virus levels in the blood and using drugs to stop that virus from reproducing. When drugs stop working, virus levels in the blood rise and physicians typically respond by changing medications. However, effective drugs may not always be available.

"Results from the current study suggest that if a patient is failing their current treatment, and other effective drugs are not available, then it may be best to take advantage of the virus' lessened ability to kill CD4 T cells, by staying on the same medication" says Dr. Badley. "We have begun to study whether the best approach might be instead to monitor Casp8p41 levels as opposed to measuring virus levels, and use that to determine whether or not to change treatment."

Researchers have already developed a way to measure Casp8p41 in the blood of patients, and this new knowledge may ultimately lead to a new diagnostic tool for HIV treatment, based upon predicting whether a

patient's virus will deplete CD4 T cells.

Provided by Mayo Clinic