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Dosage of HIV drug may be ineffective for half of African-Americans

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Many African-Americans may not be getting effective doses of the HIV drug maraviroc, a new study from Johns Hopkins suggests. The initial dosing studies, completed before the drug was licensed in 2007, included mostly European-Americans, who generally lack a protein that is key to removing maraviroc from the body. The current study shows that people with maximum levels of the protein—including nearly half of African-Americans—end up with less maraviroc in their bodies compared to those who lack the protein even when given the same dose. A simple genetic test for the gene that makes the CYP3A5 protein could be used to determine what doses would achieve effective levels in individuals, the researchers say.

The results of the small study were published online on Aug. 12 in the journal *Drug Metabolism and Disposition*.

"Because African-Americans are disproportionately affected by HIV infection, it is doubly important that we get the dosing right," says Namandje Bumpus, Ph.D., an assistant professor of pharmacology and molecular sciences at the Johns Hopkins University School of Medicine.

CYP3A5 is a protein found in abundance in liver and intestinal cells. It adds an oxygen molecule to various drugs to make them more water-soluble so they can ultimately enter the urine and leave the body. Eighty to 90 percent of European-Americans have no CYP3A5, because they have inherited two dysfunctional copies of the CYP3A5 gene.

Normally, the absence of CYP3A5 is not noticeable; a very similar protein, CYP3A4, acts on most of the same drugs. But, for a few drugs, like maraviroc and the cancer drug vincristine, CYP3A5 seems to play a particularly prominent role in helping to remove them from the body. In those cases, the presence or absence of CYP3A5 would likely affect the amount of a drug in the bloodstream, the Johns Hopkins team predicted. And since 85 percent of participants in the maraviroc dosing study were European-Americans, who typically lack functional CYP3A5, the researchers surmised that the recommended dose for maraviroc could be too low for anyone with two functional copies of the gene—including 45 percent of African-Americans.

To test this idea, the research team grouped 24 healthy volunteers according to how many functional copies of the CYP3A5 gene they had—zero, one or two. They were each given a single dose of maraviroc in the recommended dose of 300 milligrams, and each participant's blood was taken at 10 time points over 32 hours.

At almost all time points, the concentrations of maraviroc were similar for the groups with zero or one functioning copies of CYP3A5 but were lower in those with two functioning copies. Compared to those with two poorly functioning copies of the gene, those with two functioning copies had a 41 percent lower concentration overall. Importantly, as a group, those with two functioning copies had an average concentration that was just above the lowest level determined to be effective against the virus. And four of the eight had individual average concentrations that dropped below that.

"The trend we saw was that the more functional CYP3A5 a person had, the faster maraviroc was processed and left the body, so the lower its concentration in the bloodstream," explains Bumpus. "What's nice is that, if a larger study confirms that we are underdosing this group, a simple genetic test prior to dosing decisions could rectify the situation."

She adds that this study highlights the importance of designing clinical trials in which the participants are as ethnically diverse as the population to be treated.

More information: Cytochrome P450 3A5 Genotype Impacts Maraviroc Concentrations in Healthy Volunteers, dx.doi.org/10.1124/dmd.114.060194

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