# HIV-1 drug resistance mutations associated with increased risk of antiretroviral treatment failure

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An analysis of data from 10 studies indicates that the presence of low frequency (also called "minority") human immunodeficiency virus type 1 (HIV-1) drug resistance mutations, particularly those involving nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, are significantly associated with an increased risk of first-line antiretroviral treatment failure, according to an article in the April 6 issue of *JAMA*.

Using traditional tests, the prevalence of transmitted drug resistance mutations is estimated to be between 8 percent and 16 percent among HIV-1 infected persons in North America and Europe. These tests may fail to detect the presence of low-frequency, or minority, drug resistance mutations, according to background information in the article. "Presence of these minority variants may adversely affect the response to antiretroviral treatment (ART), but their clinical significance continues to be the subject of considerable debate and uncertainty," the authors write.

Jonathan Z. Li, M.D., of Brigham and Women's Hospital and Harvard Medical School, Boston, and colleagues conducted a systematic review and pooled analysis to examine the relationship between the presence of baseline low-frequency HIV-1 drug resistance mutations and the risk of virologic failure with NNRTI-based regimens in treatment-naive (had not previously received treatment) adults. The authors identified 10 studies that met criteria for the primary analysis, which included data for

985 participants.

Low-frequency drug resistance mutations were detected in 187 participants, including 117 of 808 patients in the cohort studies. The researchers found that low-frequency HIV-1 drug resistance mutations were associated with a 2.3 times increased risk of virologic failure after controlling for medication adherence, race/ethnicity, baseline CD4 cell count, and plasma HIV-1 RNA levels. The increased risk of virologic failure was most strongly associated with NNRTI-resistant minority variants (2.6 times increased risk).

"Among participants from the cohort studies, 35 percent of those with detectable minority variants experienced virologic failure compared with 15 percent of those without minority variants. The presence of minority variants was associated with 2.5 to 3 times the risk of virologic failure at either 95 percent or greater or less than 95 percent overall medication adherence. A dose-dependent increased risk of virologic failure was found in participants with a higher proportion or quantity of drug-resistant variants," the researchers write.

Analysis indicated that the presence of a drug-resistant minority variant, overall medication adherence, and race/ethnicity were all significant independent predictors of virologic failure. Compared with white participants, those of black, Hispanic, and other races/ethnicities all had an increased risk of virologic failure. "The relationship between race/ethnicity and virologic failure may be mediated by factors such as socioeconomic status, drug and alcohol use, or other factors not accounted for here that may correlate with adherence and could contribute to residual confounding," the authors write.

The researchers add that using the most sensitive test for NNRTI resistance mutations, approximately 11 patients would need to be screened prior to initiating an NNRTI based ART regimen to avoid 1

case of virologic failure.

"These data provide a rationale for developing standardized clinical assays for the detection of NNRTI-resistant minority variants. Because NNRTI-based regimens are the most commonly prescribed first-line antiretroviral therapy, the clinical use of ultrasensitive screening for drug-resistant HIV could help identify individuals at greatest risk of virologic failure and allow ART to be tailored appropriately."

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