Replication Capacity: An Additional Measure of HIV Disease Progression?

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HIV's replication capacity (RC), a measurement of the virus's fitness, may be useful for people living with HIV and their health care providers in figuring out how quickly HIV disease will progress, according to new data published in the April 1 issue of the Journal of Acquired Immune Deficiency Syndromes (JAIDS). The study results show that untreated people living with HIV with lower, compared with higher, RC had a slower progression to a CD4 cell count below 350 cells—the widely accepted threshold for starting antiretroviral (ARV) therapy.

Decisions regarding when to start ARV therapy are based primarily on an individual's CD4 cell count. The U.S. Department of Health and Human Services (DHHS) urges treatment for all people living with HIV with CD4 cell counts below 350; it also recommends treatment for those with CD4 counts below 500 cells.

Although the loss of CD4 cells is largely determined by viral load, a recent analysis suggests that only a small percentage of the variability of CD4 cell loss can be directly attributed to the quantity of HIV in the body. RC measures the quality of virus being produced during HIV's reproduction process and is among several cofactors believed to play a role in HIV disease progression (a patient's age, HIV-specific immune responses and the presence of different coreceptors on CD4 cells are also being studied).

Impairment of RC—determined using a commercially available Monogram Biosciences test that measures how well a person's virus is able to replicate compared with a genetically "perfect" wild-type strain of HIV—has already been independently associated with a slower rate of CD4 cell loss and disease progression in a cohort of young hemophiliac patients. To explore this further, Matthew Bidwell Goetz, MD, of the Veterans Affairs of Greater Los Angeles Healthcare System and his colleagues evaluated the relationship between RC and disease progression in a large, demographically diverse cohort of people with early stage HIV infection who had not yet begun ARV therapy.

The study evaluated single RC measurements in 316 HIV-positive patients with CD4 counts greater that 450 cells, viral loads in excess of 1,000 copies per milliliter (mL), and no history of ARV therapy. The average CD4 count of those entering the study was 617 cells.

The average RC was 79 percent among the study participants. With this determined, two groups of patients were compared: one group consisting of 160 patients with an RC of 79 percent or lower and another group consisting of 156 patients with an RC higher than 79 percent.

Patients were followed in the study for an average of 51 months. During this time, individuals harboring HIV with reduced RC had a slow rate of disease progression, determined using a composite of endpoints including time to a CD4 count below 350 cells, time to the initiation of ARV therapy, or death. The difference between the two groups was statistically significant, meaning that it was too great to have occurred by chance.

Looking at each “endpoint” individually, the only difference that stood out statistically was the time to the initiation of therapy. About 10 percent of those in the lower RC group, compared with 16 percent of those in the higher RC group, started ARV therapy within the average follow-up time. There were no statistically significant differences between the two groups when looking specifically at the time to a CD4 count below 350 cells or death.

Having a lower RC was also associated with a lower viral load. Whereas those in the lower RC group had an average viral load of 4.0 log during the follow-up period, those in the higher RC group had an average viral load of 4.2 log during the follow-up period. This difference was statistically significant.

Those with a lower RC were also less likely to have any HIV mutations associated with resistance to protease inhibitors—either occurring naturally or as a result of being infected by a person with drug-resistant virus—than those in the higher RC group (2 percent versus 8 percent, respectively). This difference was statistically significant, whereas there were no statistically significant difference when comparing the presence of other mutations conferring resistance to other ARV drug classes.

Though the researchers acknowledged that their study has a number of weaknesses—notably that it only looked at RC once in this study population, whereas RC should likely be measured over time to draw firm conclusions regarding its relationship to rates of disease progression—they concluded by stating that measuring RC may be useful as an additional indicator in planning when to start ARV treatment. For this to become standard of care, however, Goetz’s group points out that further validation of this assay is needed.

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http://beta.docker.poz.com/article/hiv-replication-capacity-18149-6180