CMV Treatment May Reduce Inflammation and Improve Immune Function

The cytomegalovirus antiviral drug letermovir led to improvements in immune biomarkers and physical function in people with HIV.

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Letermovir, an antiviral drug for cytomegalovirus (CMV), was associated with reduced inflammation, improved CD4 T-cell counts and CD4/CD8 ratios and better physical function among people with HIV on effective antiretroviral treatment, according to research presented at the recent Conference on Retroviruses and Opportunistic Infections (CROI 2025) in San Francisco.

Based on these findings, lead researcher Sara Gianella Weibel, MD, of the University of California San Diego, suggested that letermovir "is probably the most exciting intervention that has been done in people with HIV for inflammation and aging over the last 20 years."

While antiretroviral treatment can suppress HIV replication indefinitely, HIV-positive people are still prone to chronic inflammation that can contribute to comorbidities such as cardiovascular disease and age-related effects such as frailty. CMV coinfection has been linked to immune activation and inflammation in people with HIV, and CMV reactivation may play a role in other conditions, such as long COVID.

Cytomegalovirus, a member of the herpesvirus family, is transmitted via bodily fluids (including saliva and urine), during sex and from mother to child. Studies suggest that around a third of children, half of middle-aged adults and up to 90% of elderly people in the United States have had CMV, with even higher rates in low- and middle-income countries.

CMV is usually asymptomatic in people with a healthy immune system. The virus goes dormant after acute infection, but it remains in the body for life and can reactivate if immunity is suppressed, potentially leading to severe illness. Before the advent of effective antiretroviral treatment, people with AIDS were susceptible to CMV colitis (gastrointestinal illness), lung and brain inflammation and retinitis that could lead to blindness.

Asymptomatic CMV infection is usually not treated, but letermovir (Prevymis) is used to prevent illness in CMV-positive people undergoing stem cell transplants and for CMV-negative recipients of

a kidney transplant from a CMV-positive donor. Medications for treating CMV illness include ganciclovir (Cytovene), valganciclovir (Valcyte), cidofovir (Vistide), foscarnet (Foscavir) and the more recently approved maribavir (Livtencity).

Reduced Inflammation

Gianella Weibel and colleagues conducted the ACTG A5383 trial, sponsored by the National Institutes of Health's AIDS Clinical Trials Group, to evaluate whether letermovir would improve immunological and functional aging-related outcomes among people with HIV who tested positive for CMV and were on suppressive antiretroviral therapy. Senior investigator Peter Hunt, MD, of the University of California San Francisco, and his team have been studying CMV in people with HIV for more than a decade; they previously reported that eight weeks of valganciclovir reduced immune activation in a small trial.

Study participants were randomly assigned to receive letermovir along with their antiretroviral therapy or antiretrovirals alone for 48 weeks. The study initially aimed to enroll 180 people, with a planned futility analysis when the first 40 participants reached week 8.

This early analysis included 39 participants. About three quarters were men, half were white, nearly 40% were Black and the median age was approximately 58 years. The median CD4 T-cell count was approximately 385, and more than 40% had a count below 350.

This analysis showed that people in the letermovir group had an unexpected increase in soluble tumor necrosis factor receptor 2 (sTNFR2)—a biomarker associated with inflammatory diseases—at week 8. Under the assumption that this early rise would predict later outcomes, the trial was stopped early.

But the researchers continued to follow participants on letermovir through week 48, observing a sustained reduction in interleukin 10 (IL-10) receptor activity as well as declines in several proteins associated with cardiovascular disease and cancer. After the temporary rise, sTNFR2 levels declined significantly between weeks 8 and 48 in the letermovir group. Similar patterns were observed for the pro-inflammatory cytokine IL-6 and the inflammation biomarkers C-reactive protein and D-dimer. Letermovir also led to an early and sustained reduction in IL-1-beta, another pro-inflammatory cytokine linked to cardiovascular disease and cancer mortality.

As a possible explanation for these findings, Gianella Weibel noted that CMV produces a viral version of IL-10 similar to the human anti-inflammatory cytokine IL-10, which helps the virus hide from the immune system. "We believe when we started letermovir and blocked CMV replication, we also blocked viral IL-10, which was like taking the foot off the brake of the immune system," she said.

As expected, letermovir suppressed mucosal CMV shedding in semen, throat, rectal and cervical samples. During treatment, there were only two samples (both semen) with detectable CMV DNA in the letermovir group. CMV shedding remained suppressed for up to 12 weeks after stopping the drug. CMV DNA was undetectable in all plasma samples tested during the study. CMV-specific

antibody titers declined during letermovir treatment but started rising again after the drug was stopped, suggesting that the immune system was starting to sense the virus in the early posttreatment period even though CMV shedding remained suppressed, Gianella Weibel said.

Improved Immune Function

Another study presented at the conference showed how CMV infection affects immune function. Raynell Lang, MD, of the University of Calgary, and colleagues compared immunological outcomes among more than 2,500 HIV-positive people starting antiretroviral treatment; 91% tested positive for CMV. Those with a low CD4 count or low CD4/CD8 ratio at baseline were excluded from the analysis. A higher CD4/CD8 ratio indicates better immune function; a ratio below 1 suggests impaired function.

Over 10 years of follow-up, CMV-positive and CMV-negative people were equally likely to reach a CD4 count of 500 or more (84% versus 85%, respectively). However, the CMV-positive group was less likely to achieve a CD4/CD8 ratio of 1 or higher (53% versus 72%). After two years of viral suppression, the median CD4 count and CD4/CD8 ratio were consistently higher in the CMV-negative group.

“We identified a high seroprevalence of CMV among people with HIV, which was associated with a reduced CD4+/CD8+ ratio normalization, suggesting CMV seropositivity is associated with persistent immune activation and inflammation among people with HIV who maintain HIV viral suppression on ART,” the study authors concluded.

In Gianella Weibel’s trial, people in the letermovir group experienced a greater increase in their CD4 count, which was especially pronounced—a median gain of 93 cells—among those with a count below 350 at baseline. The letermovir group also saw a significantly larger increase in the CD4/CD8 ratio, particularly among women.

What’s more, physical function improved in the letermovir group at 48 weeks, as indicated by a timed chair-rise test (how fast someone can sit in a chair and stand back up five times), which correlated with increased CD4/CD8 ratio. The study abstract noted that there was also a trend toward improvement in other functional outcomes, such as grip strength and walking speed, in this group.

Letermovir was generally safe and well tolerated, though some participants experienced diarrhea and headache. “There was no evidence of serious safety concerns related to letermovir,” Gianella Weibel reported.

“Letermovir initially increased some inflammatory markers but ultimately resulted in sustained reductions in inflammation, improved CD4/CD8 ratios and enhanced physical function/leg strength in people with HIV with CMV on suppressive ART,” the researchers concluded. “These findings suggest that suppression of asymptomatic CMV with a CMV-specific inhibitor may improve aging-related outcomes.”

Discussing her findings, Gianella Weibel said that, in retrospect, it was probably a mistake to stop the trial early, but hopefully, these results will inform and support a larger study.

Routinely offering letermovir for treatment of asymptomatic CMV in people with HIV is currently not feasible due to the drug's high cost. Other CMV medications, such as valganciclovir, are less expensive but have side effects that make them unsuitable for long-term treatment. Letermovir "has a much better safety profile, so if we can bring the cost down, I think letermovir will be a much better candidate," she said.

Gianella Weibel described one study participant, a longtime immunological nonresponder with a CD4 count around 200, who saw her count rise to 800 for the first time while taking letermovir. "She was so sad when the study was interrupted and she had to go off letermovir that her CD4s dropped down," Gianella Weibel recalled. "We might not have to treat everyone," she suggested. "We might be able to stratify and just pick the people that would take the most advantage—for example, women with a low CD4 [count]."

"This is an important finding and ACTG is especially excited because there are currently no interventions that improve immune recovery and functional status in people living with HIV who are taking effective antiretroviral therapy," ACTG Chair Joseph Eron, MD, of the University of North Carolina Chapel Hill, said in a statement. "Larger studies are needed to confirm these results; if they do, this intervention could represent a significant breakthrough in HIV and aging research."

[This report has been updated to add a comment from ACTG chair Joseph Eron.]

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