Can Semaglutide Slow Aging and Improve Cognition in People With HIV?

GLP-1 agonists have beneficial effects beyond weight loss, but they're not reaching those who need them most.

April 23, 2025 By Liz Highleyman

Semaglutide and related weight-loss medications may help reduce inflammation, improve cognitive function and gut health, reduce alcohol use and even slow biological aging in people living with HIV, according to studies presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2025).

Weight gain and metabolic abnormalities are a growing concern for people with HIV as they age, raising the risk for cardiovascular disease, fatty liver disease and other health problems.

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide (Ozempic or Wegovy), mimic a natural hormone that suppresses appetite, regulates insulin and blood sugar and slows emptying of the stomach. Originally developed to treat type 2 diabetes, these drugs are now widely used to manage obesity. They have been shown to reduce the risk of heart and kidney disease and some types of cancer, and ongoing research continues to show additional—sometimes unexpected—benefits.

"While we know some of the types of benefits [related to] metabolic health, this new data points to potential aging benefits. It suggests that GLP-1 agonists may be helpful in stabilizing biological aging in a subset of people living with HIV," investigator Michael Corley, PhD, of the University of California San Diego, said at the conference.

Epigenetic Aging

A study funded by the National Institutes of Health (NIH) looked at outcomes among HIV-positive people with lipohypertrophy, or abnormal abdominal fat accumulation. Visceral fat, or adipose tissue, deep within the abdomen is more strongly associated with cardiovascular disease and other health problems than subcutaneous fat under the skin.

Grace McComsey, MD, of Case Western Reserve University, and colleagues assessed the effects of semaglutide in 108 adults on suppressive antiretroviral therapy with overweight or obesity and a large waist circumference or waist-to-hip ratio. About 60% were men, a majority were Black, the

median age was 52 and the median CD4 T-cell count was around 800.

The participants were randomly assigned to receive subcutaneous injections of semaglutide (ramping up the dose to 1.0 milligrams) or a placebo once weekly for 32 weeks. CT and DEXA scans were used to measure total, visceral and subcutaneous fat, lean body mass and body composition.

As reported at IDWeek 2023 and in The Lancet Diabetes & Endocrinology, people taking semaglutide experienced notable declines in weight, total body fat and visceral abdominal fat, while those in the placebo group saw little change or slight gains. About two thirds of semaglutide recipients achieved at least 5% weight loss. What's more, semaglutide recipients showed favorable changes in biomarkers of inflammation. Semaglutide was generally well tolerated, with side effects similar to those seen in the general population (mainly gastrointestinal).

At CROI, Corley presented results from a secondary analysis looking at the effects of semaglutide on epigenetic aging biomarkers. Epigenetics refers to changes in gene expression that are not attributable to modification of the DNA sequence itself. For example, DNA methylation involves addition of methyl group molecules to DNA, which can either silence or activate genes. The researchers used various DNA methylation epigenetic clock algorithms to calculate epigenetic age.

This analysis included a subgroup of 84 participants. A majority (58%) were men, the mean age was 49 and they had been living with HIV for 19 years, on average. The current mean CD4 count was high (762), but the mean lowest-ever count was just 211, indicating serious immune suppression.

At baseline, the participants had an increased epigenetic age, greater predicted mortality risk and a steady pace of aging. Over 32 weeks of treatment, the pace of biological aging slowed by about 9% in the semaglutide group compared with the placebo group, and the annual rate of epigenetic aging mortality risk decreased by about three years.

"Semaglutide stabilized epigenetic aging in people with HIV-associated lipohypertrophy over 32 weeks on treatment," the researchers concluded.

"These findings suggest that semaglutide's favorable effects on epigenetic aging biomarkers may not be due simply to changes in inflammation or baseline adiposity measures, but potentially more fundamental impact on some of these hallmarks of aging," Corley said. "Longitudinal studies looking at the long-term impact are going to be the most critical studies moving forward."

In a related analysis, Alina Pang, PhD, of Weill Cornell Medicine, and colleagues looked at epigenetic indicators of health, aging and physical fitness in HIV-positive people with metabolic dysfunction-associated steatotic liver disease (MASLD)—the new name for non-alcoholic fatty liver disease. Only one drug is currently approved for the more severe stage of MASLD (metabolic dysfunction-associated steatohepatitis, or MASH), and management largely relies on lifestyle

changes such as weight loss and exercise, but GLP-1 agonists show promise.

The SLIM LIVER trial (ACTG A5371), also funded by the NIH, enrolled 51 adults on suppressive antiretroviral therapy with a large waist circumference, insulin resistance or pre-diabetes and MASLD. They self-administered semaglutide injections once weekly for 24 weeks, again ramping up the dose to 1.0 mg.

As reported at last year's CROI, semaglutide reduced liver fat by about a third. Over half of participants had at least a 30% reduction in intrahepatic triglyceride content, and more than a quarter experienced complete MASLD resolution. This was accompanied by significant weight loss, reduced waist circumference and improvements in fasting glucose and triglyceride levels. Women, older people and Latino and white participants tended to see greater reductions in weight and liver fat. Around 20% did not respond to semaglutide, comparable to the proportion in the general population.

In the new analysis presented this year, Pang's team used an epigenetic clock that incorporates maximum oxygen uptake, walking speed and grip strength to estimate biological age in 41 people with available data. Although the mean chronological age was 52 years, the average estimated epigenetic age was about 10 years older. Participants with weaker grip strength at baseline or greater improvement in grip strength after 24 weeks on semaglutide saw a larger decrease in liver fat after controlling for sex and chronological age. These findings suggest that epigenetic biomarkers may help predict clinical response to semaglutide in people with HIV, according to the researchers.

Cognitive Function

In another analysis from the lipohypertrophy study, Ornina Atieh, MD, of Case Western Reserve University, and colleagues investigated the effect of semaglutide on neurocognitive function, asking whether changes in fat or inflammatory markers could explain the drug's benefits.

The researchers used Cognivue, an FDA-approved computer-based test, to evaluate cognitive function at baseline and after 32 weeks on semaglutide. This comprehensive tool assesses several cognitive components including visual-spatial ability, attention and executive function, naming and language, memory and abstraction, as well as reaction time and processing speed.

The overall Cognivue scores were similar in the semaglutide and placebo groups, but people taking semaglutide had significantly better visual-spatial and delayed recall scores, and there was a trend toward better naming and language performance. However, after adjusting for sex and CD4 count, only visual-spatial scores remained close to statistical significance.

The researchers found that neither weight nor visceral adipose tissue could explain semaglutide's effect on visual-spatial performance after adjusting for other factors. In contrast, levels of high-sensitivity C-reactive protein (a biomarker of inflammation) and sCD163 (a marker of macrophage activation) were correlated with better scores.

“Semaglutide has shown a potential beneficial impact on cognitive function, specifically the visuospatial cognitive subdomain in people living with HIV,” the researchers concluded. “This effect appears to be mediated by the effect of the drug on attenuating inflammation and not on adiposity.”

Gut Health

Another SLIM LIVER analysis looked at the effects of semaglutide on the gut microbiome—the ecosystem of bacteria and other microorganisms that live in the intestines. Prior studies have shown that imbalances in the microbiome can weaken the gut lining and trigger chronic inflammation.

Stephanie Dillon, PhD, of the University of Colorado, and colleagues reported that participants who used semaglutide showed an overall increase in the diversity and abundance of microbes associated with good gut heath. But people with certain preexisting microbiome features had a smaller reduction in liver fat while taking semaglutide, suggesting that microbiome-targeted therapies might be used along with GLP-1 agonists to enhance clinical outcomes in people with MASLD.

Alcohol Use

In addition to their effects on metabolism, there’s growing evidence that GLP-1 agonists act on the brain to reduce not only appetite for food but also cravings for alcohol, tobacco and recreational drugs. Some semaglutide users have even reported that it reduced their urge to gamble.

Heidi Crane, MD, MPH, of the University of Washington Seattle, and colleagues looked at changes in alcohol use among people with HIV in routine clinical care who were receiving semaglutide for diabetes or weight management. The analysis included 443 people in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort who received care at eight sites across the United States after April 2018. More than three quarters were men, 43% were white, 35% were Black, 18% were Latino and the median age was 54. People who didn’t drink alcohol at baseline were not included.

The researchers found that people who were prescribed semaglutide had lower levels of alcohol use compared with those not taking the drug. This was particularly the case for people considered to have higher-risk alcohol consumption.

“Additional evaluation of the role of GLP-1 receptor agonists as medications for alcohol use and other substance use disorders is needed,” the researchers concluded.

Studies of semaglutide and related drugs for management of alcohol use and drug addiction are already underway for the general population. These findings underscore the need to include people with HIV in such research.

As with most aspects of HIV care, there are disparities in access to semaglutide. The drug costs

around $1,000 per month or more, depending on the dose, and many private insurers and state Medicaid programs do not cover it for weight loss.

In another CNICS analysis, Andrew Hahn, MD, of the University of Washington Seattle, and colleagues evaluated the use of semaglutide among people with HIV, assessing potential disparities based on race and ethnicity.

The researchers identified CNICS participants who were eligible for semaglutide due to obesity (a BMI of 30 or higher) or diabetes (HbA1c of 6.5% or higher) between 2019 and 2023. The researchers identified 11,617 people who met at least one of these criteria. Of these, 74% were men, 35% were white, 48% were Black and the median age was 53.

Within this group, only 774 people (7%) were prescribed semaglutide, with higher rates in the later part of the study period. Black people with HIV were less likely to receive semaglutide compared with their white peers, despite the fact that they accounted for a larger proportion of those who qualified. Of those who received semaglutide, 75% were men, 41% were white and 36% were Black.

Overall, Black people were 20% less likely than white people to receive semaglutide. Latino people were also less likely to be prescribed semaglutide, but the difference did not reach the threshold for statistical significance. However, both Black and Latino people were substantially less likely than white people to receive semaglutide for diabetes.

“Our findings were not driven by unequal severity of diabetes. Black people with HIV had higher average HbA1c values than other groups and made up 48% of the semaglutide-indicated group, but 36% of those who received [it],” the researchers noted. “This treatment gap may exacerbate existing inequalities and disproportionate comorbidity burden by race groups.”

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