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Commentary

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With the introduction of combination antiretroviral therapy (ART) and increasingly obesogenic environments around the world, the rate of overweight or obesity in people with HIV (PWH) has increased.[1] Importantly, PWH previously treated with some first generation antiretrovirals exhibit lipohypertrophy characterized by the disproportionate accumulation of body fat in visceral adipose tissue (VAT), contributing to increased inflammation and altered metabolism of glucose and lipid, and exacerbating the risk of cardiometabolic complications, such as diabetes and cardiovascular diseases.[1]

Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin analogues that regulate appetite and promote weight loss in overweight or obese patients with or without diabetes.[2] Moreover, these drugs reduce visceral fat and waist circumference in addition to improving glycemic control and cardiovascular outcomes in the population without HIV.[2,3] In addition to traditional risk factors, PWH face unique viral and ART-associated risk factors for cardiometabolic diseases. In recent studies of PWH, semaglutide has demonstrated a similar degree of weight loss as in the general population,[4] as well as reduction in VAT and subcutaneous adipose tissue (SAT).[5] Given these properties, GLP-1 receptor agonists have the potential to be a novel therapy for HIV-associated lipohypertrophy, as well as obesity.

In *The Lancet Diabetes & Endocrinology*, Allison Eckard and colleagues[6] report the first phase IIb randomized, double-blind, placebo-controlled trial that investigated the effects of semaglutide treatment on HIV-associated lipohypertrophy for the duration of 32 weeks in 108 adults with controlled HIV. The participants had body mass index $\geq$25 kg/m^2 and evidence of lipohypertrophy as characterized by increased waist circumference and waist-to-hip ratio but were without diabetes. The semaglutide arm initiated weekly 0.25 mg subcutaneous injections and uptitrated over 8 weeks to the 1 mg dose administered over the subsequent 24 weeks. Semaglutide compared to placebo resulted in a substantial reduction in abdominal adipose tissue, with a larger 31% reduction in VAT compared to 11% decrease in SAT. The absence of significant reduction in the waist-to-hip ratio with concomitant greater limb fat loss with semaglutide versus placebo suggests a global pattern of body fat reduction. Importantly, semaglutide conferred a significantly higher reduction in hemoglobin A1c and triglyceride levels compared to placebo. However, similarly to the effects evident in the general population, there was 5.7% reduction in the lean body mass with semaglutide treatment in the study.

The most profound effect of semaglutide in the trial[6] was the significant loss of the abdominal VAT. Disproportionate visceral adiposity is a hallmark of HIV-associated lipohypertrophy, and such form of adiposity is associated with insulin resistance, dyslipidemia, chronic inflammation, and increased mortality in PWH.[7] Therefore, the effect of semaglutide on VAT may potentially translate to reduction in the risk of cardiometabolic diseases in PWH. In an open-label study, semaglutide reduced intrahepatic triglyceride levels and improved glucose and lipid profiles in 51 PWH.[8]

However, there remains concerns regarding the adverse effects of semaglutide, especially those pertaining to gastrointestinal disorders – ranging from the commonly encountered symptom of nausea to pancreatic and gallbladder diseases. Lipase elevations and cholelithiasis observed in the semaglutide arm preserve the concerns regarding the risks of pancreatitis and cholecystitis in PWH, as in the general population.[9]

Importantly, the dose of semaglutide in the trial was 1.0 mg weekly – the maximum dose approved by the U.S. Food and Drug Administration at the time of the study.[6] With the approval of 2.4 mg weekly dose,[10] examining the safety and incremental efficacy of the higher dose would be warranted. Moreover, the sustainability of the VAT reduction upon cessation of semaglutide

would be important to study in HIV-associated lipohypertrophy. Whether semaglutide has differential effects in PWH with long-term lipohypertrophy versus those with recent weight gain following initiation of or switch to certain antiretroviral drugs, such as tenofovir alafenamide or integrase strand transfer inhibitors[1], would also be crucial to understand. Lastly, additional data on semaglutide is needed to understand the impact of reduction in VAT and lean body mass on the risk of cardiometabolic complications, as well as sarcopenia, frailty, and mortality in PWH.

In conclusion, the trial demonstrates the efficacy of semaglutide in the reduction of abdominal VAT in PWH.[6] There does not appear to be unique semaglutide-associated adverse effects in PWH compared to the general population, albeit at the 1.0 mg weekly dose studied. Overall, semaglutide has the potential to be an important drug to treat HIV-associated lipohypertrophy. PWH are an aging population predisposed to cardiometabolic complications, and the role of semaglutide in the population would further be informed with additional safety data at higher doses and assessment of its efficacy on long-term cardiometabolic outcomes.

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