# HIV and Endocrine Dysfunction

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HIVC

# Endocrine System

- Your endocrine system consists of the tissues (mainly glands) that create and release hormones.

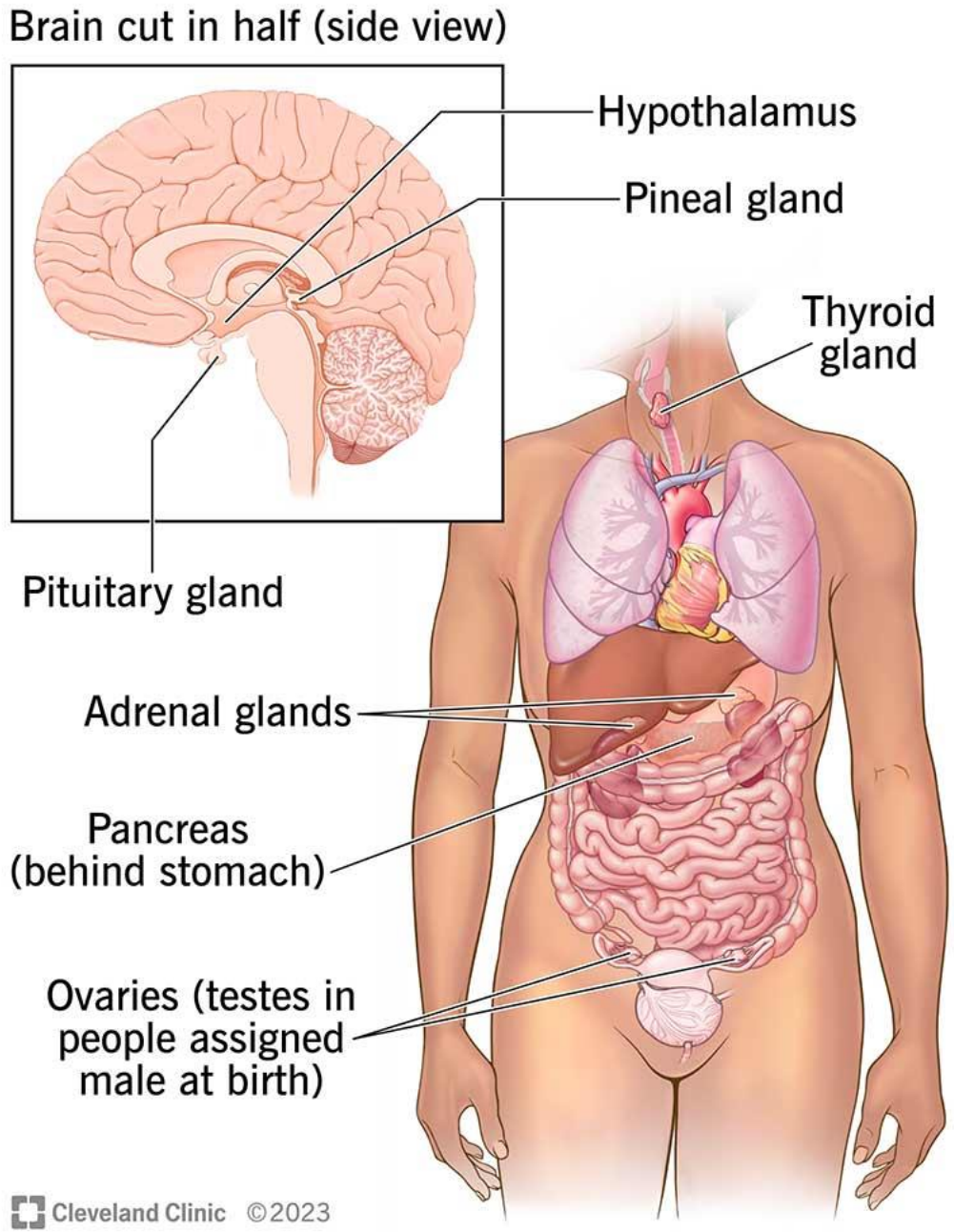
- Hormones are chemicals that coordinate different functions in your body by carrying messages through your blood to your organs, skin, muscles and other tissues. These signals tell your body what to do and when to do it. Hormones are essential for life and your health.

# Endocrine System

- The main function of your endocrine system is to release hormones into your blood while continuously monitoring the levels. Hormones deliver their messages by locking into the cells they target so they can relay the message. You have more than 50 different hormones, and they affect nearly all aspects of your health — directly or indirectly. Some examples include:

- Metabolism.
- Homeostasis (constant internal balance), such as blood pressure and blood sugar regulation, fluid (water) and electrolyte balance and body temperature.
- Growth and development.
- Sexual function.
- Reproduction.
- Sleep-wake cycle.
- Mood.
- Very small amounts of hormones can trigger significant responses and changes in your body. If your body has too little or too much of a hormone, it affects your health. This often causes noticeable symptoms.

# Endocrine system



# Endocrine System Glands

- Pineal gland: This is a tiny gland in your brain that's beneath the back part of your corpus callosum. It makes and releases the hormone melatonin.
- Pituitary gland: This is a small, pea-sized gland at the base of your brain below your hypothalamus. It releases eight hormones, some of which trigger other endocrine glands to release hormones.
- Thyroid gland: This is a small, butterfly-shaped gland at the front of your neck under your skin. It releases hormones that help control your metabolism.
- Parathyroid glands: These are four pea-sized glands that are typically behind your thyroid. Sometimes they exist along your esophagus or in your chest (ectopic parathyroid glands). They release parathyroid hormone (PTH), which controls the level of calcium in your blood.
- Adrenal glands: These are small, triangle-shaped glands on top of each of your two kidneys. They release several hormones that manage bodily processes, like metabolism, blood pressure and your stress response.

# Endocrine System Organs

- Hypothalamus: This is a structure deep within your brain (which is an organ). It's the main link between your endocrine system and your nervous system. It makes two hormones that your pituitary gland stores and releases (oxytocin and vasopressin) and makes and releases two hormones (dopamine and somatostatin).
- Pancreas: This organ is in the back of your abdomen (belly). It's both an organ and a gland and is also part of your digestive system. It releases two hormones that are essential to maintaining healthy blood sugar levels: insulin and glucagon.
- Adipose tissue (body fat): This is a connective tissue that extends throughout your body. It's found under your skin (subcutaneous fat), between your internal organs (visceral fat) and in the inner cavities of bones (bone marrow adipose tissue). Adipose tissue releases many different hormones, including leptin, angiotensin and adiponectin.
- Ovaries: These are small, oval-shaped glands located on either side of your uterus. They produce and store your eggs (also called ova) and make sex hormones that control your menstrual cycle and pregnancy.
- Testicles (testes): These are small, round organs underneath your penis in your scrotum. They make sperm and sex hormones, particularly testosterone.

# Other Hormone-Releasing Tissues

- Digestive tract (stomach and small intestine): Your digestive tract is the largest endocrine-related organ system. It makes and releases several hormones that play a role in your metabolism. Examples include gastrin and ghrelin.
- Kidneys: Your kidneys are two bean-shaped organs that filter your blood. They're part of your urinary system, but they also produce hormones, like erythropoietin and renin.
- Liver: Your liver is part of your digestive system, but it also produces hormones, including insulin-like growth factor 1 (IGF-1) and angiotensinogen.
- Heart: When your blood pressure rises, your heart releases two hormones called A-type natriuretic peptide and B-type natriuretic peptide.

# Male Hypogonadism

- Hypogonadism has been recognized among HIV-infected men early on in the HIV epidemic. Despite increased efficacy of HIV treatment, the prevalence of hypogonadism, mainly secondary hypogonadism, is higher in HIV-infected men compared with non-infected controls, in the order of 9% to 16% according to recent studies [19].

- The leading cause of gonadal dysfunction in HIV-infected men relates to the effects of severe illness, weight loss, and undernutrition on gonadotropin secretion. Predisposing factors include age, obesity, and insulin resistance, particularly in men with visceral adiposity.

- In HIV-infected patients with advanced disease secondary hypogonadism may be caused by opportunistic infections affecting the pituitary or hypothalamus. In such patients a pituitary/hypothalamic magnetic resonance imaging is recommended [20].

- In HIV-infected men, as in the general population, chronic HCV infection resulting in chronic liver disease is associated with hypogonadism [21]. In this setting, the diagnosis of hypogonadism may be confounded by the characteristically elevated sex hormone binding globulin (SHBG) levels found in patients with chronic liver disorders.

# Male Hypogonadism

- Primary hypogonadism is reported less often. In a large Italian cohort, Rochira et al. [19] reported low morning testosterone associated with elevated gonadotropin levels in 16% of young patients, with a median age of 45 years. Possible mechanisms causing primary hypogonadism may involve direct cytokine effects on the testes. Tumor necrosis factor (TNF) inhibition of side-chain cleavage enzyme, as well as interleukin 1 (IL-1) inhibition of Leydig cell steroidogenesis and luteinizing hormone binding to the Leydig cell have been reported [19].

- Although up to 25% of AIDS patients suffer opportunistic infections, including CMV and toxoplasmosis, involvement of the testes in these cases have rarely been reported. Data suggesting development of primary hypogonadism secondary to testes involvement by systemic neoplasms, Kaposi sarcoma, and testicular lymphoma are sparse [16]. When an infectious process is suspected in HIV-infected men presenting with primary hypogonadism, a scrotal ultrasound should be performed.

# Female Hypogonadism

- In HIV-infected women, hypogonadism presenting as amenorrhea is common, occurring in approximately 25% of patients. Anovulation is seen in up to 50% of HIV-infected women with reduced cluster of differentiation 4 (CD4) counts. Reduced in gonadotropin synthesis and secretion in the context of the stress of illness is the most probable culprit. Early menopause has been reported in up to 8% of HIV-infected women [22].

- Reduced androgen levels are often seen in HIV-infected women. The cause of androgen deficiency in the context of HIV may be explained in part by intra-adrenal shunting toward cortisol production and away from androgen production, especially in the presence of weight loss.

# Bone Disorders

- Multiple studies have shown a higher prevalence of osteoporosis and increased risk of fragility fractures in HIV-infected patients compared with healthy subjects. Current data suggest that immunologic factors such as activation of T-cells, low CD4 cell count, and coinfection with hepatitis B and C are strongly associated with reduced bone density, particularly in women.

- HIV infection in itself is considered a risk factor for osteoporosis and fragility fractures. It causes T-cell activation and production of pro-inflammatory cytokines including TNF-α, IL-6, receptor activator of nuclear factor kappa-B ligand (RANKL), and other soluble immune factors that enhance activity of osteoclasts, resulting in increased bone resorption [31]. The levels of endogenous inhibitors of osteoclastogenesis including osteoprotegrin and interferon γ are downregulated in advanced HIV infection. HIV proteins such as Tag and Nef reduce the amount of mesenchymal stem cell (MSC) precursors that can proliferate into osteoblasts by inducing MSC senescence, leading to decreased bone formation [16].

- Endocrine factors including hypogonadism, relative GH deficiency and vitamin D deficiency may further contribute to reduced bone density in HIV-infected patients. Lipoatrophy may mediate bone loss as well, through a complex relationship between central signaling of adipocyte hormones and bone [16]. Impaired parathyroid hormone (PTH) secretion and action have also been reported in HIV-infected patients [32].

# ART and Bone Disorders

- The initiation of ART is associated with a decrease in bone mineral density (BMD) of 2% to 6% over a time period of 96 weeks. This bone loss is not reversible and is independent of the specific ART regimen used [33].

- Some ART medications, particularly tenofovir disoproxil fumarate (TDF), and PIs have direct deleterious effects on BMD. TDF may augment phosphate reabsorption in the proximal tubule (Fanconi's syndrome), leading to secondary increase in PTH and bone turnover. Osteomalacia is an additional skeletal complication that occurs in this context [34]. A different formulation of tenofovir, tenofovir alafenamide (TAF), is less deleterious to bone compared with TDF. Vitamin D deficiency may occur through various mechanisms: impairment of 1-α-hydroxylase may be secondary to treatment with PIs, whereas efavirenz may reduce cytochrome P450 2RI expression, leading to decreased 25-hydroxylation of vitamin D. Further, conversion of vitamin D into its inactive metabolites is promoted by the same mechanism [35].

- IRIS following the initiation of ART has also been implicated in bone loss. The rapid improvement in immune function leads to an increase in cytokine levels, as well as to systemic or local inflammation that may also contribute to bone loss. The magnitude of CD4-recovery has been shown to positively correlate with the increase in bone resorption markers [16].

# Osteoporosis Screening in PWH

- In view of the above, dual-energy X-ray absorptiometry screening is recommended earlier (postmenopausal women and men >50 years of age) in HIV-infected patients relative to the general population (>65 for men and >70 years of age for women).

# Osteoporosis Treatment

- Strategies to attenuate bone loss include calcium and vitamin D supplementation, as well as life-style changes such as smoking cessation and weight-bearing exercise. Co-morbidities known to adversely affect bone health such as hypogonadism should be corrected. Importantly, substitution of TDF and/or PIs by other treatment regimens is an important strategy leading to improved bone health in HIV-infected patients [36]. Switching TDF to other ART regimens (including TAF, abacavir, or raltegravir) has been shown to increase BMD by 1% to 3% over 48 to 96 weeks, but effects on fracture risk are not available.

- Bisphosphonates are the first line therapy for osteoporosis in HIV-infected patients. Alendronate and zoledronate, have been evaluated for the treatment of osteoporosis in HIV patients. Inhibition of bone turnover markers and an increase in bone density in lumbar spine and hip were consistently achieved, but there is no data on fracture prevention. A single dose of intravenous zoledronic acid prior to initiation of ART has been shown to prevent treatment-associated bone loss [36]. Studies to evaluate other, non-bisphosphonate medications such as PTH analogs and denosumab were not specifically studied in HIV-infected patients [16].

# Metabolic Changes and Dyslipidemia

- The prevalence of cardiovascular disease (CVD) in HIV-infected patients is higher compared with HIV-uninfected controls. This can be attributable to an increased prevalence of traditional CVD risk factors in addition to the effects of chronic inflammation. Dyslipidemia has been documented in up to 54% of patients with HIV [16].

- Lipid abnormalities are particularly common in patients with lipodystrophy syndrome, characterized by changes in fat distribution, with increased visceral and upper trunk fat. Hypertriglyceridemia, related in part to an increased secretion and decreased clearance of very low-density lipoprotein (VLDL), has long been associated with HIV infection and was observed prior to the introduction of ART [37,38]. As reported in longitudinal studies, a significant decrease in total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol are observed following seroconversion [39]. With ART initiation, total and LDL cholesterol return to baseline, pre-infection levels, but low HDL levels usually persist [39]. Among patients with changes in fat distribution, 57% had hypertriglyceridemia and 46% low HDL in comparison with a matched cohort from the Framingham Offspring Study [40]. Some studies suggest an increase in atherogenic small dense LDL in patients with HIV associated lipodystrophy.

# ARTs and Dyslipidemia

- ART play a role in the development of dyslipidemia, although modern regimens have less metabolic toxicities than those used in the early ART era. Treatment with PIs may be associated with dyslipidemia in 28% to 80% of patients. Dyslipidemia is more common with lopinavir/ritonavir, tipranavir and fosamprenavir, but less frequently associated with darunavir and atazanavir use. Possible mechanisms of PI induced dyslipidemia include inhibition of adipocyte differentiation and lipogenesis, decreased clearance of chylomicrons and VLDL, and increased synthesis of triglycerides by the liver. Among the non-nucleoside reverse transcriptase inhibitors (NNRTIs) the most common drug associated with dyslipidemia is efavirenz, in contrast with rilpivirine, etravirine, and nevirapine that in general do not cause this side effect.

- Thymidine analog nucleoside reverse transcriptase inhibitors (NRTIs; stavudine, didanosine, and zidovudine) which are rarely used in the current ART regimens, are associated with lipid dyscrasias and lipoatrophy, while newer NRTIs, abacavir and tenofovir, have neutral or even favorable effects on lipids profile. For example, the combination of TDF and emtricitabine may lower total and LDL cholesterol and triglycerides. Integrase standard transfer inhibitors (INSTIs) such as raltegravir and dolutegravir are more lipid neutral

# Statins and PWH

- For People With HIV Who Have Low-to-Intermediate (<20%) 10-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimates

- Age 40–75 Years
- When 10-year ASCVD risk estimates are 5% to <20%, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) recommends initiating at least moderate-intensity statin therapy (AI).
- Recommended options for moderate-intensity statin therapy include the following:
- Pitavastatin 4 mg once daily (AI)
- Atorvastatin 20 mg once daily (AII)
- Rosuvastatin 10 mg once daily (AII)
- When 10-year ASCVD risk estimates are <5%, the Panel favors initiating at least moderate-intensity statin therapy (CI). The absolute benefit from statin therapy is modest in this population; therefore, the decision to initiate a statin should take into account the presence or absence of HIV-related factors that can increase ASCVD risk.a
- Same options for moderate-intensity statin therapy as recommended for 10-year ASCVD risk estimates of 5% to <20% (see above)
- Age <40 Years
- Data are insufficient to recommend for or against statin therapy as primary prevention of ASCVD in people with HIV. In the general population, lifestyle modifications are recommended for people age <40 years, with statin therapy considered only in select populations (see American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines).

# Statins and PWH

- For People Age 40–75 Years Who Have High (≥20%) 10-Year ASCVD Risk Estimates

- Initiate high-intensity statin therapy.
- For People Age 20–75 Years Who Have Low-Density Lipoprotein Cholesterol (LDL-C) ≥190 mg/dL

- Initiate high-intensity statin therapy at maximum tolerated dose.
- For People Age 40–75 Years With Diabetes Mellitus

- Initiate at least moderate-intensity statin therapy. Perform further risk assessment to consider using a high-intensity statin.

# Statin Therapy-Key Considerations

- Coadministration of certain statins and antiretroviral drugs may result in significant drug–drug interactions. In some cases, the interaction may require statin dose adjustment, switching to another statin, or increased monitoring for statin-related adverse effects (see the Drug–Drug Interaction section below for details).
- Initiation of statin therapy should be deferred in pregnant individuals at low-to-intermediate ASCVD risk until after pregnancy, and statin therapy should be discontinued if a person with HIV becomes pregnant. Breastfeeding is not recommended while a person is on statin therapy.

# Diabetes Mellitus and PWH

- Insulin resistance and DM are not uncommon among HIV-infected patients. The reported prevalence of DM is between 2% to 14% [16]. Insulin resistance is considered the primary mechanism for impaired glucose tolerance and DM in these patients. Increased body mass index, lipodystrophy, low CD4 counts and exposure to older ARTs, including stavudine and indinavir, are predictive of DM in this patient population [42].

- There are multiple mechanisms involved in the development of insulin resistance in HIV-infected patients. Abnormal fat distribution, loss of peripheral subcutaneous fat, altered cytokines (e.g., low adiponectin and leptin, increased soluble TNF receptor 1), mitochondrial dysfunction, increased lipolysis and hepatic and muscle fat accumulation may be involved [43]. ln addition, altered function of CD4+ and CD8+ T-cells may impair glycolysis. Damage to the structural barrier of the gastrointestinal tract may occur in chronic HIV infection, leading to increased microbial translocation. The associated inflammation may persist even after ART initiation and despite viral suppression. The chronic inflammation state, is associated with metabolic dysfunction, increased risk of development DM and cardiovascular morbidity [44].

# Hemoglobin A1c (HbA1c) and PWH

- Hemoglobin A1c (HbA1c) underestimates glycemia in HIV-infected patients by 0.2% to 0.5%. This is thought to be due to low-grade hemolysis, higher mean corpuscular volume, NRTI use (specifically abacavir), and reduced CD4 count. It is suggested to obtain HbA1c prior to and within 1 to 3 months after starting ART and repeat testing every 6 to 12 months while using HbA1c threshold cutoff of 5.8% for the diagnosis of DM

# ARTs and Insulin Resistance

- PIs increase insulin resistance by inhibiting the transport function of glucose transporter type 4 thus decreasing glucose uptake and insulin secretion. Newer PIs (darunavir and atazanavir) have limited influence on insulin sensitivity [16]. Some NRTIs are associated with insulin resistance, due to mitochondrial toxicity or through effects on subcutaneous fat [45].

- If the patient develops DM while treated with ARTs, consideration should be given to switch the therapeutic regimen, particularly if it consists of lopinavir/ritonavir or a thymidine analog (zidovudine, stavudine).

- Type 2 diabetes should be managed in the HIV-infected population according to current guidelines for the general population. There are few interactions between DM medications and PIs, with the exception of saxagliptin, which should be avoided. On the other hand, dolutegravir may increase metformin concentration, and in case of co-administration the total daily dose of metformin should be limited to 1,000 mg and careful monitoring is required [16].

# Lipodystrophy

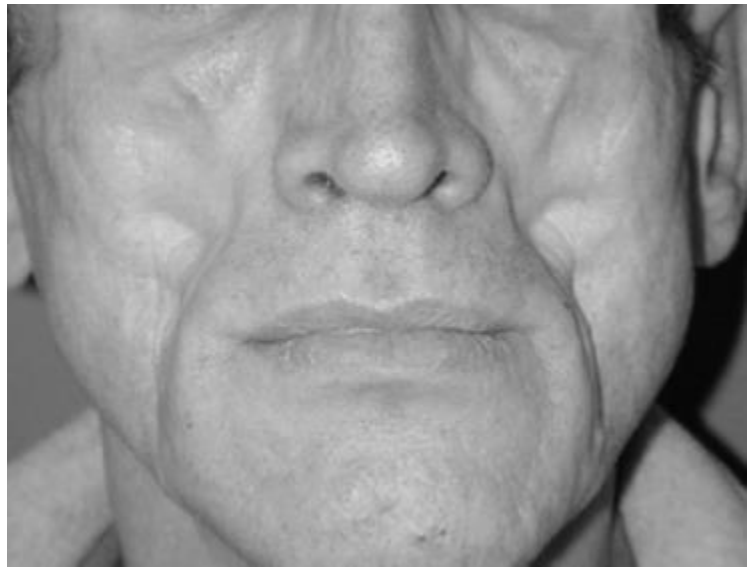
- Prior to the availability of effective ART, severe wasting and decreased levels of cholesterol were common metabolic abnormalities in advanced AIDS patients [46]. After the introduction of effective ART, the prevailing metabolic abnormalities are secondary to central fat accumulation and peripheral fat loss. The term “HIV-associated lipodystrophy syndrome” was coined, but today it is clear that this is not a single syndrome but rather the co-occurrence of phenotypes that vary from person to person. Some individuals present with lipoatrophy, others have fat accumulation, and some have a mixed picture [47]. These morphologic changes are associated with metabolic complications such as disorders in glucose and lipid metabolism.

# Lipoatrophy

- Lipoatrophy involves the loss of subcutaneous fat in the face, arms, legs, abdomen, and/or buttocks. Unlike AIDS-associated wasting, loss of subcutaneous fat in lipoatrophy is not associated with loss of lean body mass. Metabolic complications including dyslipidemia and dysglycemia are common in patients with lipoatrophy, and its presence should prompt evaluation for these conditions. HIV disease severity and host factors (age, baseline body type) may influence the risk of lipoatrophy, but the main etiology is iatrogenic.

- Effect of medications on lipoatrophy development
- The main risk factor for development of lipoatrophy is exposure to thymidine analogs NRTIs, (stavudine more than zidovudine). Although these are not first-line NRTI drugs used today, some patients who started treatment many years ago may still be taking this medication. These medications are also still used in some resource-limited settings.

- The underlying mechanism of lipoatrophy development may be a NRTI-induced inhibition of mitochondrial DNA polymerase and mitochondrial toxicity, leading to adipocyte apoptosis. Biopsies of subcutaneous adipose tissue from patients with lipoatrophy are characterized by depletion of mitochondrial DNA, inflammation, and apoptosis.



# Fat accumulation-lipohypertrophy

- HIV-associated fat accumulation is mainly visceral, while subcutaneous fat tissue remains normal or may decrease. Fat accumulation in HIV is characteristically central, including abdominal visceral adipose tissue (VAT) deposition with increased abdominal girth, and fat accumulation in the dorsocervical area, trunk, and upper chest. This pattern of fat accumulation is often associated with dyslipidemia and insulin resistance. Patients of both genders may develop breast fat deposition or subcutaneous lipomas. Fat accumulation can occur to some degree with any ART regimen, being prevalent in up to 70% of patients [49].

- Interestingly, lipoatrophy may coexist with fat accumulation. The association between lipodystrophy and metabolic abnormalities in HIV-infected patients may be mediated by changes in several adipokines. Adiponectin levels are low, secondary to decreased adipocyte differentiation [50,51]. Lower leptin levels were documented in patients with significant lipoatrophy compared with HIV-infected patients without lipoatrophy [52]. However, there is no absolute leptin threshold that is associated with metabolic abnormalities. Finally, a single nucleotide polymorphism in the resistin gene, which has been previously linked to DM in obese patients, was found in HIV-infected patients who developed significant body composition and metabolic changes on ART

# Lipohypertrophy Treatment Options

| Intervention | Dose | VAT outcome |
|---|---|---|
| Diet and exercise | Individualized aerobic training program x 4 months | Reduction in VAT by 12% |
| | Home exercise training program x 4 months | Decrease in waist circumference, but no change in VAT |
| Metformin | Metformin 500mg bid vs. placebo x 3 months | Reduction in VAT by 6.3% |
| | Metformin 500mg bid (increased to 850mg bid) +/− exercise training x 3 months | Decreased VAT by 8.5% |
| | Metformin 500mg bid (increased to 1500mg bid) vs. placebo x 6 months | Decrease in truncal fat by 14.6%, but no significant decrease in VAT |
| Human Leptin | Recombinant human leptin at 0.01 mg/kg bid x 3 months, then 0.03 mg/kg bid x 3 months | Average reduction in VAT by 32% after 6 months |
| Recombinant human growth hormone | rhGH 4mg daily vs. placebo x 12 weeks induction | Reduction in VAT by 20.3% |
| | rhGH 0.028 IU/kg/day vs. placebo x 6 months | Reduction in truncal fat but no specific data on VAT |
| Tesamorelin (growth hormone-releasing factor) | Tesamorelin 2mg daily vs. placebo x 26 weeks | Reduction in VAT by 15.2% |
| | Tesamorelin 2mg daily vs. placebo x 6 months (efficacy phase) | Reduction in VAT by 10.9% |

# GLP-1 Receptor Agonists as Lipohypertrophy Treatment in PWH

- Semaglutide holds promise as an effective treatment for HIV-associated lipohypertrophy. The potential risk of serious adverse events deserves further scrutiny in large trials in people with HIV.

Semaglutide in people with HIV-associated lipohypertrophy

The Lancet Diabetes & Endocrinology, Volume 12, Issue 8, August 2024, Pages 504-505 Y Joseph Hwang, Todd T Brown, Jacqueline Capeauer scrutiny in large trials in people with HIV.