Review

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Immunometabolic reprogramming *via* GLP-1 receptor agonists in people with HIV: A multidimensional systemic framework

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SUMMARY: Antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition, but pathological weight gain, adipose dysfunction, and persistent inflammation are increasingly prevalent among aging people with HIV (PWH). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 RAs have emerged as transformative therapies, although PWH were underrepresented in pivotal trials. This review integrates randomized trials, observational cohorts, pharmacogenomic studies, and emerging mechanistic evidence within a framework of GLP-1-mediated immunometabolic reprogramming. HIV-specific trials demonstrate reductions in visceral adiposity, body weight, inflammatory biomarkers, and liver fat. Exploratory or preliminary studies suggest possible effects on gut epithelial integrity, immune-cell trafficking, lymphoid pyroptosis, and DNA-methylation aging measures; however, several of these findings remain conference-level, preprint, or post hoc evidence and require prospective validation. We also examine lean-mass loss, weight regain after discontinuation, pharmacogenomic variation, drug access, and research priorities. Overall, GLP-1 RAs are promising components of cardiometabolic care for PWH, but immunologic, gerotherapeutic, and HIV-reservoir applications should currently be considered hypothesis-generating.

Keywords: visceral adiposity, metabolic dysfunction-associated steatotic liver disease, epigenetic clocks, inflammaging, gut barrier, HIV reservoir

1. Introduction

The widespread implementation of combination antiretroviral therapy (ART) has markedly prolonged the life expectancy of people with HIV (PWH), shifting the clinical focus from AIDS-defining opportunistic infections to chronic, non-communicable comorbidities (*1*). Modern antiretroviral regimens, particularly those containing integrase strand transfer inhibitors (INSTIs, such as dolutegravir, bictegravir, or cabotegravir) and tenofovir alafenamide (TAF), while achieving superb rates of virologic suppression, are frequently accompanied by significant weight gain and adipose tissue dysfunction (*2-4*). Although initial post-ART weight gain often represents a physiological "return-to-health" phenomenon in advanced patients, long-term follow-up reveals that aging, polypharmacy including frequent antidepressant use, smoking cessation, and Western lifestyles synergistically drive undesirable, persistent, and pathological obesity, most notably among those with low baseline CD4+ T-cell counts (*3*).

In ART-treated PWH, persistent low-grade systemic inflammation and pathological obesity act synergistically to drive cardiovascular-kidney-metabolic (CKM) syndrome (*5-7*). This clinical entity is characterized by visceral adiposity, type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), arterial hypertension, and accelerated atherosclerosis, collectively compromising comorbidity-free healthspan (*5-8*). Consequently, identifying metabolic interventions that combine profound weight-lowering efficacy with systemic anti-inflammatory properties is a premier clinical priority in modern HIV medicine (*1,5*).

Recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide, liraglutide, and the

dual GIP/GLP-1 receptor co-agonist tirzepatide, have revolutionized the management of obesity and T2DM (*9,10*). By mimicking endogenous incretin hormones, GLP-1 RAs delay gastric emptying and act directly on the hypothalamic arcuate nucleus to enhance satiety and suppress appetite (*9-11*). In HIV-negative populations, semaglutide achieves a ~15% reduction in body weight (*9*) and reduces the risk of major adverse cardiovascular events (MACE) by 20% in overweight or obese adults without diabetes (*12*). Moreover, the landmark FLOW trial demonstrated a 24% reduction in composite renal outcomes in patients with T2DM and chronic kidney disease (CKD) (*13*).

However, because PWH were systematically excluded from early registrational trials, clinicians have faced a relative dearth of evidence specific to this high-risk population (*12,13*). In reality, the biological impact of the GLP-1 receptor pathway in chronic HIV infection extends far beyond simple weight loss and glucose homeostasis. Recent reviews have begun to synthesize emerging evidence on GLP-1 RAs in PWH, highlighting weight gain mechanisms specific to this population, clinical considerations for GLP-1 RA use, and the potential for cardiometabolic risk reduction (*14,15*). However, these prior clinical studies, including Phase 2b trials (*16*), focused primarily on clinical endpoints without providing an integrated framework linking GLP-1 receptor agonist-mediated immunometabolic reprogramming with geroscience dimensions.

This review develops a translational framework of 'GLP-1-mediated immunometabolic reprogramming' by evaluating clinical trials, real-world cohorts, and emerging mechanistic studies on visceral adipose remodeling, intestinal barrier biology, lymphoid pyroptosis, and epigenetic aging (*16-22*). Evidence maturity varies substantially across these domains; conference abstracts, preprints, and post hoc analyses are identified explicitly. By contrasting GLP-1 RAs with alternative metabolic strategies, we aim to provide a calibrated scientific basis for metabolic management and future research in PWH.

2. Literature Search Strategy

To ensure methodological rigor, we conducted a comprehensive narrative search of PubMed, MEDLINE, EMBASE, and ClinicalTrials.gov databases from inception through April 2026. We utilized combinations of the following Medical Subject Headings (MeSH) terms and free-text keywords: "GLP-1 receptor agonist", "semaglutide", "tirzepatide", "liraglutide", "obesity", "diabetes", "cardiovascular disease", "NAFLD/MASLD", "CKM syndrome", "inflammaging", "epigenetic clocks", "gut barrier", "immune activation" and "people with HIV". Our screening prioritized double-blind, randomized controlled trials (RCTs), prospective and retrospective multi-center clinical cohorts, and established clinical guidelines. To capture the latest advances in this rapidly evolving field, we integrated newly presented oral abstracts and posters from the 2024–2026 Conference on Retroviruses and Opportunistic Infections (CROI) and major national and international hepatology and cardiology symposia, explicitly qualifying these citations as preliminary conference evidence where applicable to maintain scientific transparency.

3. Main findings: Immunometabolic reprogramming *via* GLP-1 receptor agonists in PWH

3.1.1. Adipose tissue pathophysiology and CKM syndrome under ART

The prevalence of obesity (BMI ≥ 30 kg/m²) among ART-treated PWH in North America rose from approximately 14% in 2000 to 28% in 2018 (*23,24*). This rising obesity prevalence has been similarly documented in PWH across Western countries and Southeast Asia (*25*). Women living with HIV bear a disproportionately higher metabolic risk: a pooled analysis of three ART-naive trials demonstrated that women gained a mean BMI of 1.91 kg/m² over 96 weeks, compared with 1.39 kg/m² in men ($P < 0.001$), with the most substantial weight gain occurring within the first year of ART initiation (*2*). Early weight gain typically plateaus approximately two years after treatment initiation, after which weight trajectories parallel those observed in the general population (*26*).

Although population-level obesity trends among PWH mirror those of the general population, African ancestry, advanced age, lower baseline $CD4^+$ T cell counts, and higher pretreatment viral loads represent independent predictors of excessive ART-associated weight gain (*24*). ART-associated weight gain is tightly linked to lipohypertrophy, characterized by disproportionate visceral adipose tissue (VAT) accumulation (*27*). In obese PWH, VAT accounts for nearly one-quarter of total abdominal fat, a pattern strongly associated with insulin resistance and chronic inflammation (*16*). Prior exposure to thymidine analogues (*e.g.*, stavudine) has caused irreversible subcutaneous adipose tissue (SAT) loss (lipoatrophy), resulting in a mixed body composition phenotype characterized by central visceral fat excess and peripheral fat wasting in long-term PWH survivors (*28*).

Visceral fat depots undergo extensive immune cell infiltration, secreting high levels of inflammatory adipokines (*e.g.*, leptin, TNF-α, and IL-6) while suppressing anti-inflammatory adiponectin (*28,29*). Long-term exposure to INSTIs has been shown to exert proadipogenic and profibrotic effects and induce insulin resistance in human and simian adipose tissues (*29*). This localized adipocyte-driven inflammation, superimposed on HIV-mediated persistent systemic immune activation, establishes an "immunometabolic vicious cycle" that accelerates endothelial damage, impairs post-receptor insulin signaling, and induces glomerular sclerosis,

ultimately promoting the full spectrum of CKM syndrome (*5-7*).

3.1.2. Efficacy in VAT and Intrahepatic Triglyceride Clearance

In the phase 2b SLIM LIVER trial evaluating weekly semaglutide (1 mg/week) in PWH with MASLD, semaglutide achieved a 31% relative reduction in intrahepatic triglyceride (IHTG) content over 24 weeks ($P < 0.001$). Complete resolution of hepatic steatosis was observed in 29% of participants. Furthermore, abdominal MRI sub-studies confirmed a significant 15.2% reduction in VAT volume and a 12.4% reduction in SAT (*17*). Tirzepatide, evaluating dual GIP/GLP-1 agonism, demonstrated even greater efficacy in early real-world PWH series, achieving up to 18.5% total body weight loss at 48 weeks (*30*).

3.1.3. Anthropometric Discrepancies and Lean Mass Considerations

While GLP-1 RAs produce substantial body weight reductions in PWH, clinician vigilance is warranted regarding the composition of weight lost. Given that PWH inherently face an elevated baseline risk for sarcopenia, frailty, and sarcopenic obesity due to chronic low-grade inflammation and legacy antiretroviral toxicities, progressive reductions in skeletal muscle mass (SMM) during rapid weight loss may compromise physical function. Thus, clinical implementation of GLP-1 RAs in PWH should routinely incorporate structured resistance exercise regimens and optimized nutritional support (1.2–1.5 g protein/kg/day) to preserve lean mass and functional status (*17,27,37*).

3.2. Efficacy discrepancy: Reconciling RCTs with real-world cohorts

3.2.1. Visceral de-fatting efficacy in clinical trials

The double-blind, randomized, placebo-controlled phase 2b trial led by Eckard *et al*. provides high-quality level-1b evidence on the efficacy of GLP-1 RAs in PWH with central lipohypertrophy (*16*). In this 32-week study, 108 overweight/obese PWH without diabetes received weekly subcutaneous semaglutide (titrated to 1.0 mg) or placebo (*16*). Semaglutide induced a mean weight reduction of 10.4% (versus 2.3% in the placebo group; $P < 0.001$), accompanied by a 30.6% reduction in abdominal VAT area ($P = 0.0017$) and a 9.32 cm reduction in waist circumference ($P < 0.0001$) (*16*). These results demonstrate that under optimal trial conditions, the visceral de-fatting efficacy of GLP-1 RAs in PWH is highly robust and fully comparable to that observed in HIV-negative cohorts (*16*). Additionally, the SLIM LIVER trial corroborated these findings, reporting a 6.7 cm decrease in waist circumference after 24 weeks of semaglutide therapy (*17*). The detailed efficacy outcomes of this landmark trial are summarized in Table 1 (*16*).

Furthermore, subgroup stratifications reveal that PWH with concomitant T2DM achieve more modest weight loss (typically 3–5%) compared to non-diabetic PWH (7–10%) (*10,18*). This efficacy attenuation aligns with general population trends, driven by central GLP-1 resistance and altered receptor desensitization kinetics in diabetic states.

3.2.2. Real-world efficacy dilution: Biological and pharmacogenomic drivers

In contrast, real-world cohort studies reveal lower average effectiveness than tightly controlled trials (*18,30*). In the multicenter CNICS cohort (Haidar *et al*.), 222 PWH achieved a mean weight loss of 5.7% after 12 months of semaglutide (*18*). Similarly, in the UCSD single-center cohort analyzed by Nguyen *et al*. ($N = 225$), GLP-1 RA therapy yielded a mean weight reduction of 5.4 kg, and tirzepatide use was associated with higher odds of achieving at least 5% weight loss than semaglutide use (OR = 5.46) (*30*). Preliminary CROI 2026 data from the Washington, DC cohort (O'Connor *et al*., abstract 695; $N = 362$) showed that 30.4% achieved at least 5% weight loss at 6-12 months; participants with diabetes had lower adjusted odds of reaching the 5% and 10% thresholds. These real-world findings identify three principal biological and clinical considerations (*10,19,29*):

Table 1. Key efficacy outcomes of semaglutide in HIV associated lipohypertrophy (32 Week RCT)

Outcome Endpoint	Semaglutide ($n = 54$)	Placebo ($n = 54$)	Change (95% CI)	P
Body weight change (%)	-10.40%	-2.30%	-8.1% (-10.88, -5.32)	< 0.001
Abdominal VAT area (cm^2)	-30.60%	No significant change	-30.82 cm^2 (-50.13, -11.51)	0.0017
Total body fat (ln kg)*	-18.90%	-	β = -0.21 (-0.34, -0.05)	0.0009
Waist circumference (cm)	-8.30%	-	-9.32 cm (-12.10, -6.54)	< 0.0001
HbA1c (%)	-0.47%	-	-0.47% (-0.67, -0.28)	< 0.0001
HOMA-IR (ln unit)	-43.00%	-	β = -0.56 (-1.04, -0.08)	0.0238

**Note*: β coefficient represents the estimated treatment effect on the natural logarithmic scale (ln kg or ln unit) derived from linear mixed-effects models adjusted for sex and treatment-by-time interactions. CI: confidence interval; VAT: visceral adipose tissue; HOMA-IR: homeostatic model assessment for insulin resistance.

(1). *Confounding by comorbid diabetes*: In a real-world cohort, 82% of patients present with comorbid T2DM (*30*). In diabetic states, target tissue GLP-1 receptor expression is downregulated, and patients exhibit advanced insulin resistance, which blunts central satiety signaling, resulting in significantly lower weight-loss efficacy compared to patients with obesity alone (*10,19*).

(2). Pharmacogenomic and ancestral variations: Real-world data indicate that Black patients achieve less weight loss on GLP-1 RAs than White patients (*19*). A landmark GWAS by Su *et al*. provided a genetic explanation for this disparity, identifying a missense variant in the signal peptide region of GLP1R (rs10305420, p. Pro7Leu) where each additional allele is associated with an extra -0.76 kg of body weight reduction ($P = 2.9 \times 10^{-10}$) (*19*). However, this "booster" allele is highly prevalent in European ancestry populations (~40%) but is found in only 7% of African ancestry populations, predisposing Black patients to a genetically blunted therapeutic response (*19*).

(3). Potential role of adipose tissue fibrosis and remodeling: PWH treated with INSTIs such as dolutegravir or raltegravir can develop a pathologically altered adipose tissue phenotype (*29*). Long-term INSTI exposure has been associated with increased fibrosis in subcutaneous and visceral adipose tissue, periadipocyte collagen deposition, adipocyte hypertrophy, and altered adipogenic and insulin-sensitizing pathways. Whether these histological changes translate into clinically meaningful resistance to GLP-1 RA-mediated fat loss in humans remains an open question and warrants dedicated investigation (*29*).

We also note the combination of GLP-1 RAs with growth hormone-releasing hormone (GHRH) analogs like tesamorelin (*31*) and emerging multi-agent strategy discussions (*32*). A comprehensive summary of key HIV-specific studies, categorized by OCEBM evidence levels and clinical recommendation strengths, is presented in Table 2 (*16-21,30,33*), supported by retrospective CNICS analyses showing liver fibrosis score improvements (*33*).

3.3. Gut mucosal integrity and compartmentalized immune reconstitution

Table 2. Summary of key HIV-specific studies of GLP-1 RAs

Study & Year	Study Design & Sample Size	Evidence Level (OCEBM)	Intervention	Key outcomes and evidence interpretation
Eckard *et al*. 2024 (*16*)	RCT, placebo-controlled, *N* = 108	Level 1b	Semaglutide 1.0 mg SC weekly × 32 wk	VAT -30.6%, weight -10.4%, and hsCRP -39.9%. Randomized phase 2b evidence for body-composition and inflammatory outcomes.
Lake *et al*. (SLIM LIVER) 2024 (*17*)	Single-arm, open-label, *N* = 51	Level 2b	Semaglutide 1.0 mg SC weekly × 24 wk	IHTG -31.3% and 29% MASLD resolution. Single-arm open-label evidence.
Haidar *et al*. (CNICS) 2024 (*18*)	Retrospective cohort, *N* = 222	Level 2b	Semaglutide (real-world practice)	Weight -5.7% at 12 months and HbA1c -1.07% in participants with T2DM. Retrospective cohort evidence.
Nguyen *et al*. (UCSD) 2024 (*30*)	Retrospective cohort, *N* = 225	Level 2b	GLP1 RAs / Tirzepatide	Weight -5.4 kg; tirzepatide associated with higher odds of at least 5% weight loss. Retrospective cohort evidence.
Su *et al*. (GWAS) 2026 (*19*)	Genome-wide association, *N* = 27885	Level 2b (observational association)	GLP1 RAs/ Tirzepatide	GLP1R rs10305420: -0.76 kg/allele; GIPR rs1800437 associated with nausea/ vomiting risk. Research-stage associations; no validated genotype-guided dosing recommendation.
Marin *et al*. (CROI 2026)*(*20*)	Mechanistic pilot substudy (Preliminary conference abstract), *N* = 5	Unrated	Liraglutide SC × 8 mo	Duodenal CD4+ T-cell increase and CD69+ reduction in a small mechanistic substudy. Preliminary conference evidence; hypothesis-generating.
Corley *et al*. (2026) (*21*)	Post hoc analysis of RCT, *N* = 84	Level 2b	Semaglutide *vs* placebo	Exploratory post hoc analysis of a phase 2b RCT; not a clinical treatment recommendation.
Ma *et al*. 2026 (*33*)	Retrospective cohort, *N* = 1850	Level 2b	Semaglutide	FIB-4 score -0.11 in moderate-to-advanced fibrosis and -0.64 in advanced fibrosis. Observational pre/post evidence.

*Preliminary conference evidence applies to Marin *et al*. only; findings await peer-reviewed publication. DM: diabetes mellitus; hsCRP: high-sensitivity C-reactive protein; IHTG: intrahepatic triglyceride; OCEBM: Oxford Centre for Evidence-Based Medicine; OR: odds ratio; RCT: randomized controlled trial; SC: subcutaneous.

3.3.1. The circulating CD_4^+ T-cell paradox

A multi-center clinical cohort study in Germany evaluating PWH treated with dulaglutide or semaglutide reported a statistically significant, non-time-dependent decrease in circulating CD4+ T-cell counts, with a median decline of approximately -60 cells/μL ($P = 0.035$) (*34*). Crucially, this decline was restricted to the CD4+ T-cell compartment, as circulating CD8+ T-cell counts, plasma cytokines, and viral suppression remained entirely unaffected (*34*), most notably among individuals with low baseline CD4+ counts. While this initial finding raised concerns regarding potential incretin-mediated immunosuppression, tissue-level investigations suggest a possible compartmentalized mucosal phenomenon rather than cell depletion (*20,34*).

3.3.2. Preliminary signals of mucosal barrier repair and immune modulation

In a preliminary pilot mechanistic study presented at CROI 2026 (Marin *et al*., oral abstract 115, preliminary conference evidence; $N = 5$), paired duodenal and colonic mucosal biopsies were evaluated in PWH before and after liraglutide therapy (*20*):

Physical Barrier Repair: Liraglutide therapy induced progressive reconstruction of duodenal microvilli, accompanied by the significant upregulation of genes governing epithelial differentiation (CDX2, VIL1) and tight junction integrity (OCLN, TJP1) (*20*). This exploratory finding suggests potential mitigation of the "leaky gut" pathology that persists in PWH despite suppressive ART (*35,36*).

Exploratory mucosal T-Cell dynamics: Duodenal CD4+ T-cell frequency increased from 12% at baseline to 24% post-treatment ($P < 0.01$), while the proportion of highly activated CD69+ mucosal T-cells dropped from 74% to 13% (*20*). Given the unblinded pilot design and extremely small sample size ($N = 5$), these quantitative shifts represent early mechanistic signals rather than definitive proof of tissue-level immune reconstitution (*20,34*).

3.3.3. Hypothesis-generating nature of mucosal homing dynamics

The observation of declining peripheral CD4+ T-cell counts alongside preliminary signals of increased mucosal CD4+ T cells in a small pilot cohort supports a speculative hypothesis of compartmental redistribution (*20,34*). Given that chronic HIV infection persistently compromises the intestinal barrier and promotes microbial translocation despite suppressive ART (*35,36*), it is hypothesized that GLP-1 RAs may modulate gut endothelial adhesion molecules (such as MAdCAM-1), encouraging α4β7+CCR9+ CD4+ T-cell recruitment into the lamina propria. However, because this model relies on a pilot conference abstract ($N = 5$), the α4β7/CCR9 homing axis must be strictly categorized as a hypothesis-generating concept (*20,34,37*). Well-powered, prospective clinical trials with expanded tissue-biopsy cohorts are required to validate these mucosal dynamics.

3.4. Cardio-kidney-metabolic (CKM) protection and inflammatory decay

3.4.1. Anti-inflammatory decay and endothelial preservation

Persistent chronic inflammation is a key driver of accelerated cardiovascular disease in PWH on suppressive ART (*5,6*). In the Eckard RCT, 32 weeks of once-weekly semaglutide led to a dramatic and statistically significant reduction in systemic and vascular inflammatory biomarkers (*16*):

High-Sensitivity C-Reactive Protein (hsCRP): Percent change of -39.92% ($P = 0.01$, 95% CI: -0.87 to -0.15), dropping the median baseline hsCRP from a high-cardiovascular-risk state (4.04 μg/mL) toward a safer target (*16*).

Soluble CD163 (sCD163): Percent change of -12.10% ($P = 0.05$, 95% CI: -0.26 to 0.001), indicating a substantial cooling of vascular macrophage activation (*16*).

Interleukin-6 (IL-6): Percent change of -18.84% ($P = 0.07$, 95% CI: -0.44 to 0.02) (*16*).

These findings were corroborated by Funderburg *et al*., confirming that the anti-inflammatory effects of semaglutide were weight-independent, pointing to a direct, receptor-mediated immunomodulatory action of GLP-1 RAs (*38*). In terms of calculated risk, semaglutide treatment resulted in a 33% reduction in the 10-year ASCVD risk score ($P = 0.026$) (*16*).

3.4.2. Cardiorenal and hepatic protection

In the prospective, single-arm, open-label phase 2b SLIM LIVER pilot trial (ACTG A5371, Lake *et al*.), 24 weeks of dose-escalated semaglutide led to a -31.3% relative reduction in intrahepatic triglyceride (IHTG) content, with complete MASLD resolution (defined as IHTG < 5%) achieved in 29% of participants ($P < 0.0001$) (*17*). This hepatic clearance was accompanied by a 5.8% decrease in waist circumference and a 10.5% decrease in plasma triglycerides (*17*). Key endpoints of the SLIM LIVER study are summarized in Table 3 (*17*).

In a general-population systematic review and meta-analysis, GLP-1 RA therapy was associated with a slower annual decline in eGFR and a 24% reduction in microalbuminuria; HIV-specific renal outcome data remain limited (*39*). These findings are directionally consistent with cardiorenal benefits reported in large general-population trials (*13,40,41*). In PWH, cardiovascular risk-score changes should be interpreted cautiously (*16,42*). Preliminary CROI 2026 findings from Ross Eckard *et*

Table 3. Key endpoints of the SLIM LIVER study (24 weeks of semaglutide)

Outcome Endpoint	Baseline	Week 24	Absolute change (95% CI)	Relative change	*P*
IHTG (%)	12.7 ± 6.1%	8.5 ± 4.7%	-4.2% (-5.4, -3.1)	-31.30%	< 0.0001
Body weight (kg)	103.0 ± 20.8kg	95.1 ± 22.8kg	-7.8kg (-9.5, -6.1)	-8.10%	< 0.0001
Waist circumference (cm)	115.0 ± 11.8cm	108.0 ± 12.9cm	-6.7cm (-8.2, -5.1)	-5.80%	< 0.0001
HOMA-IR	5.4 ± 5.1	3.9 ± 3.9	-1.5 (-3.2, 0.2)	-27.70%	0.086
Triglycerides (mg/dL)	150.0 ± 87.9	131.0 ± 75.8	-26.8 (-46.1, -7.5)	-10.50%	0.007
ALT (IU/L)	30.7 ± 13.4	24.8 ± 11.9	-6.1 (-9.7, -2.5)	-15.30%	0.001
MASLD resolution (IHTG < 5%)	0%	29%	+29.00%		< 0.001

**Note*: Baseline and Week 24 values are raw observed means ± standard deviations (SD). Absolute and relative changes are modeled estimates accounting for baseline covariates. ALT elevation defined as > 19 IU/L in females and >30 IU/L in males. ALT: alanine aminotransferase; HOMA-IR: homeostatic model assessment for insulin resistance; IHTG: intrahepatic triglyceride; MASLD: metabolic dysfunction-associated steatotic liver disease.

al. (abstract 699) reported improvement in calculated 10-year ASCVD risk but no significant 32-week change in flow-mediated dilation, pulse-wave velocity, or coronary calcium (*42*). Thus, short-term changes in risk scores may reflect metabolic and inflammatory improvement rather than established structural vascular remodeling.

3.5. Epigenetic rejuvenation and gerotherapeutic potential

3.5.1. Multi-Tissue and Systems-Based DNA Methylation Clocks

Corley *et al*. reported an exploratory post hoc DNA-methylation analysis of the randomized phase 2b trial of semaglutide in HIV-associated lipohypertrophy. Epigenetic aging was not a prespecified endpoint, but adjusted analyses identified significant between-group decelerations across multiple biological aging clocks (*21*):

PCGrimAge (High-precision mortality and healthspan clock) Decreased by -3.08 years ($P = 0.007$) (*21*).

GrimAge V2 (Multisystem chronic disease clock): Decreased by -2.26 years ($P = 0.009$) (*21*).

PhenoAge (Physiological aging clock): Decreased by -4.90 years ($P = 0.004$) (*21*).

DunedinPACE (Rate of aging clock): Decreased by -0.09 units/year, slowing the biological pace of aging by 9% ($P = 0.01$) (*21*).

OMICmAge (Multi-omic clock) & RetroAge (Transposable elements clock): Decreased by -2.20 years ($P = 0.009$) and -2.20 years ($P = 0.030$), respectively, demonstrating enhanced multi-omic healthspan optimization and transposable element heterochromatin stability (*21*).

Systems-Based Organ Clocks: Evaluation of 11 organ-system clocks demonstrated concordant decelerations across tissue compartments, highlighted by a significant reduction in composite SystemsAge (-4.17 years, $P = 0.009$), with the most prominent system-specific decelerations observed in inflammation, brain, and heart systems clocks ($P < 0.05$), highlighting multi-organ gerotherapeutic protection in PWH (*21*).

3.5.2. Organ-specific biological age deceleration

To eliminate confounding variables (*e.g.*, weight loss and baseline inflammation), deconvoluted organ-system epigenetic clocks were evaluated (*21*). In fully adjusted ANCOVA models (controlling for age, sex, BMI, hsCRP, and sCD163), semaglutide demonstrated highly significant, localized epigenetic rejuvenation (*21*):

Inflammation Clock: Decreased by -5.01 years ($P = 0.0056$), reflecting profound molecular "cooling" (*21*).

Brain Clock: Decreased by -4.99 years ($P = 0.0049$), establishing a molecular basis for evaluating GLP-1 RAs in HIV-associated neurocognitive disorders (HAND) (*21*).

Metabolic Clock: Decreased by -4.72 years ($P = 0.0090$), indicating comprehensive resetting of insulin sensitivity pathways (*21*).

Cardiovascular, Renal, and Hepatic Clocks: Decreased by -4.34 years ($P = 0.0088$), -4.20 years ($P = 0.014$), and -4.19 years ($P = 0.042$), respectively (*21*).

In exploratory analyses, 49% of semaglutide-treated participants showed an increase in epigenetic telomere-length estimates, and changes in selected aging measures were associated with 4.5-meter walk velocity (*21*). These findings do not establish cellular rejuvenation or frailty reversal and require prospective validation. Haidar and Delaney discussed the clinical implications of GLP-1 RAs in aging PWH (*15*), while Kim and Dixit reviewed the broader metabolic regulation of immunological aging (*43*). The reported biological-age measures are summarized in Table 4 (*21*).

3.6. Neurobehavioral regulation and substance use reduction

3.6.1. Central nervous system satiety and reward modulation

Tobacco and alcohol use are important behavioral treatment targets in PWH. The molecular rationale for incretin-mediated behavioral regulation involves central nervous system pathways (*44*). GLP-1 receptors are expressed in the hypothalamic arcuate nucleus and area

Table 4. Effects of semaglutide on epigenetic clocks in PWH (32-week RCT)

DNA Methylation Clock	Core Physiological Relevance	Change with Semaglutide	*P*
PCGrimAge	High-precision mortality and healthspan clock	-3.08 years	0.007
GrimAge V2	Multisystem chronic disease, mortality risk clock	-2.26 years	0.009
PhenoAge	Composite physiological aging clock	-4.90 years	0.004
DunedinPACE	Current pace/velocity of biological aging	-0.09 units/year (~9% deceleration)	0.010
OMICmAge	Multi-omics integrated biological age clock	-2.20 years	0.009
SystemsAge	Multisystem organ biological age clock	-4.17 years	0.009
RetroAge	Transposable element epigenetic clock	-2.20 years	0.030

**Note*: All clocks measure absolute biological age in years, except DunedinPACE, which is a rate-of-aging metric expressed in units per year.

Table 5. Studies evaluating GLP-1 RAs for substance use reduction in PWH

Trial Name / Reference	Drug	Target Study Population	Primary Endpoint	Status / Key Findings
GL1DER HIV RCT (NCT06351163)	Semaglutide SC	PWH with unhealthy alcohol use (*N* = 120)	Reduction in alcohol consumption, cardiovascular risk markers	Ongoing
Comprehensive Trial (NCT07221214)	Semaglutide SC	PWH with AUD (*N* = 80)	Weekly drinking days and heavy drinking days	Ongoing
CNICS cohort, Ruderman *et al.* 2026 (*45*)	Semaglutide SC	PWH who smoked cigarettes (*N* = 123)	Daily cigarette consumption reduction in PWH smokers	Published: 24% reduction in smoking intensity; 21% reported no smoking at end of follow-up

AUD: alcohol use disorder; PWH: people with HIV; SC: subcutaneous.

postrema, and GLP-1 signaling can modulate mesolimbic reward pathways involving the ventral tegmental area and nucleus accumbens (*44*).

3.6.2. Clinical real-world evidence

Clinical real-world evidence strongly supports this model:

Tobacco use: In the final peer-reviewed CNICS analysis, 123 PWH who smoked reported a mean baseline intensity of 10.5 cigarettes/day. After semaglutide initiation, smoking intensity decreased by 2.5 cigarettes/day (24%), and 21% reported no smoking at the end of follow-up (*45*).

Alcohol Use Disorder (AUD): In a nationwide registry analysis by Wang *et al*., semaglutide exposure was associated with a 36% reduction in the risk of hospitalization for alcohol use disorder (*46*).

Neuropsychiatric safety: Preliminary CROI 2026 findings from Haidar *et al*. (abstract 447) reported improvement in depressive symptoms among PWH receiving semaglutide. Because this evidence remains conference-level, it should not be interpreted as proof of an antidepressant effect.

Ongoing and reported clinical trials of GLP-1 RAs for substance use reduction in PWH are summarized in Table 5 (*45*):

3.7. Lymphoid sanctuary pyroptosis (GSDMD) and GLP-1 counter-regulation

The persistence of chronic low-grade inflammation in PWH under suppressive ART has historically lacked a unified tissue-level explanation (*22*). A landmark study by Crawford *et al*. analyzed lymph node and ileal biopsies from 20 ART-suppressed PWH (*22*). Using high-sensitivity RNAscope, they detected transcriptionally active, latent HIV vRNA+ cells in all lymph node germinal centers, despite complete plasma viral suppression (*22*). Crucially, the frequency of these tissue-resident HIV vRNA+ cells correlated directly with markers of cell-intrinsic pyroptosis—specifically cleaved gasdermin D (GSDMD+)—in lymph nodes (*22*). This suggests that low-level transcription of latent HIV in tissue sanctuaries continually drives GSDMD-mediated cell death, perpetuating chronic localized inflammation (*22*).

Crawford *et al*. also observed more GLP-1-positive enteroendocrine L cells in the ileum of PWH than in HIV-negative controls (*22*). Ileal GLP-1-positive cell density correlated directly with systemic inflammatory cytokines and inversely with lymph-node pyroptosis (*22*). These cross-sectional associations support a compensatory counter-regulatory model, but they do not demonstrate that exogenous GLP-1 RAs suppress GSDMD cleavage in PWH. Therapeutic enhancement of GLP-1 signaling should therefore be framed as a testable hypothesis rather than an established HIV-cure intervention (*22,47,48*).

3.8. Unified multi-organ topological signaling network

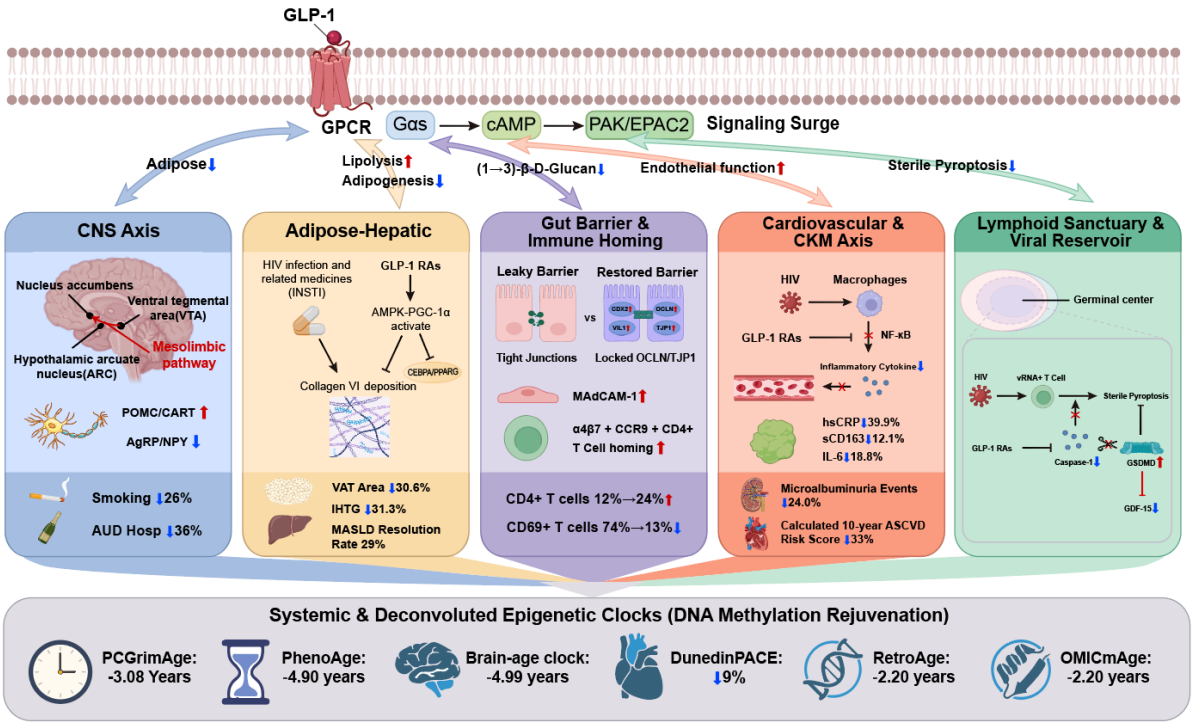

Figure 1. Multidimensional systemic framework of GLP-1 RA-mediated immunometabolic reprogramming in PWH. *Note*: Figure 1 is structured as a dual-layer topological signaling diagram depicting molecular cascades and organ-system clinical endpoints.

GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists engage canonical Gαs-coupled receptor signaling and downstream cAMP-dependent pathways (*10*). Direct immunoregulatory signaling through GLP-1R on T cells has been demonstrated mainly in preclinical alloimmune models (*48*). Together, these findings motivate—but do not yet prove—a multi-system immunometabolic model across the following compartments in ART-suppressed PWH (Figure 1):

(A) Central nervous system (CNS reward & neurobehavioral reset): Direct activation of hypothalamic arcuate nucleus (ARC) neurons (POMC/CART↑, AgRP/NPY↓) suppresses hunger, while modulation of mesolimbic dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens resets reward circuitry (*44*). This behavioral reset drives a 26.0% reduction in daily cigarette consumption (*45*), a 21.0% complete tobacco cessation rate (*45*), and a 36.0% drop in alcohol use disorder (AUD)-related hospitalizations (*46*).

(B) *Adipose and hepatic tissue (Immunometabolic fat remodeling)*: Activation of the cellular AMPK/PGC-1α metabolic axis stimulates lipophagy (*49*) and blocks integrase strand transfer inhibitor (INSTI)-induced Collagen VI matrix deposition and profibrotic transcription (CEBPA/PPARG↓) (*29*). This converts fibrotic, hyper-hypertrophic fat depots into beiged adipocytes, reducing VAT area by 30.6% (*16*) and IHTG content by 31.3% (achieving complete MASLD resolution in 29.0% of participants) (*17*).

(C) *Gut mucosal barrier preservation & immune compartmentalization*: Incretin signaling upregulates epithelial differentiation genes (*CDX2*, *VIL1*) and tight junction assembly (*OCLN*, *TJP1*), repairing leaky intestinal breaches and halting systemic lipopolysaccharide (LPS) endotoxemia (*35,36*) (Hypothesized pathway based on preliminary pilot data, $N = 5$). Concurrently, mucosal endothelial MAdCAM-1 induction recruits circulating $\alpha_4\beta_7^+CCR9^+CD4^+$ T cells back into the lamina propria, doubling mucosal $CD4^+$ T-cell density (12% to 24%) and extinguishing pathologically activated $CD69^+$ mucosal T cells (74% to 13%) (*20*).

(D) *Cardiovascular-kidney-metabolic (CKM) pathogenesis decay*: Negative regulation of vascular macrophage NF-κB pathways cools systemic endothelial inflammation, reducing hsCRP by 39.92% and sCD163 by 12.10% (*16,38*). This translates into arterial microvascular protection, lowering computed 10-year ASCVD risk scores by 33% (*16*) and reducing composite renal/microalbuminuria events by 24.0% (*39*).

(E) Lymphoid sanctuary and epigenetic aging: Persistent lymphoid HIV transcription is associated with GSDMD-mediated pyroptosis, while ileal GLP-1 upregulation may represent compensatory counter-regulation (*22*). Plasma GDF-15 is associated with HIV reservoir markers and mitochondrial stress, but a GLP-1 RA-mediated reduction in GDF-15 has not been established (*50*). Separately, an exploratory post hoc randomized-trial analysis found reductions in several DNA-methylation aging measures, including PCGrimAge and DunedinPACE (*21*).

3.9. Cross-therapeutic comparison: GLP-1 RAs *vs*. alternative metabolic interventions

Optimizing clinical decision-making for aging PWH INSTI-induced obesity and CKM syndrome mandates a head-to-head comparison between incretin mimetics and alternative therapeutic regimens (*27,28*). A "one-size-fits-all" approach is inadequate given post-ART adipose accumulation heterogeneity, legacy NRTI-induced subcutaneous lipoatrophy, and prevalent anabolic resistance (*27,28*).

Lifestyle intervention remains the nonpharmacological foundation (*27*), while metformin offers low cost and exploratory mTOR-related reservoir effects (*37,47*). In HIV-specific studies, GLP-1 RAs have shown substantial reductions in VAT and inflammatory biomarkers (*16,38*); liver-fat, epigenetic, and gut outcomes derive from open-label, post hoc, or preliminary studies and should be interpreted accordingly (*17,20,21*). Key clinical boundaries include:

Sarcopenia Mitigation: GLP-1 RA-mediated weight loss involves skeletal muscle mass reduction, mandating concurrent resistance exercise (*17,27*).

Legacy Adipose Protection: For PWH with extensive historical NRTI lipoatrophy, the depot-specificity of tesamorelin remains valuable for visceral fat reduction without worsening subcutaneous fat loss (*28,31*).

Adjuvant Reservoir Blunting: Metformin's capacity to suppress intracellular mTOR-driven proliferation provides unique utility (*37,47*).

PK/PD integrity: Bariatric surgery can alter gastric volume, pH, emptying, intestinal exposure, and bile-acid handling, which may change antiretroviral exposure in a drug-specific manner (*51-53*). Regimen review and therapeutic monitoring should be considered rather than assuming a uniform loss of absorption (*53*).

A comprehensive multidimensional comparison is detailed in Table 6 (*16,17,27,31,37,39,47,51,52*):

3.10. Discussion: Unresolved biology, clinical implementation & translational frontiers

3.10.1. Gastrointestinal tolerability and stepped titration

Gastrointestinal adverse events such as nausea, vomiting, diarrhea, and constipation are common during dose escalation (*16*). Clinical implementation considerations are reviewed by Patoulias *et al.* (*54*). Recent observational analyses have not established an overall increase in thyroid-cancer risk (*55,56*). Current semaglutide labeling contraindicates use in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 and recommends initiation at 0.25 mg once weekly with titration at 4-week intervals (*57*).

3.10.2. Sarcopenia prevention and muscle mass preservation

PWH are predisposed to sarcopenia and osteopenia due to the pro-inflammatory milieu of chronic infection, legacy antiretroviral toxicities, and aging (*27*). Clinical trials show that GLP-1 RA induced weight loss includes a significant reduction in skeletal muscle mass and psoas muscle volume (*17*). Consequently, clinicians should mandate structured resistance training (2–3 sessions weekly) and adequate protein intake (1.2–1.5 g/kg/day) during therapy (*17,27,37*).

3.10.3. Post-discontinuation metabolic rebound ("Bounce-back effect")

Obesity and CKM syndrome are chronic conditions (*58*). Discontinuing GLP-1 RA leads to rapid appetite recovery, with most individuals regaining lost weight within 1.5 years (*58*). Follow-up data from the SLIM LIVER cohort (Erlandson *et al*.) confirmed that 24 weeks after stopping semaglutide, participants experienced rapid weight regain and reversal of cardiometabolic, lipidomic, and blood pressure benefits (*59*). Real-world database analyses (Sarpatwari *et al*.) revealed that up to 75% of patients discontinue GLP-1 RAs within 12 months, influenced by out-of-pocket costs and access barriers (*60*). Short-term use is insufficient; long-term behavioral, dietary, and financial maintenance strategies are essential (*58-60*).

3.10.4. Pharmacogenomic precision medicine strategy

The GLP1R rs10305420 (p.Pro7Leu) association with treatment response and the GIPR rs1800437 (p.Glu354Gln) association with nausea or vomiting provide hypotheses for precision pharmacotherapy (*19*). However, these associations require external validation and prospective clinical-utility studies; genotype-guided drug selection, avoidance, or dose titration is not currently validated. Table 7 therefore presents these variants as research-stage companion-diagnostic candidates rather than clinical recommendations (*19*).

3.10.5. GLP-1 RAs in HIV cure and reservoir eradication strategies

The association between persistent lymphoid HIV transcription, GSDMD-mediated pyroptosis, and compensatory ileal GLP-1 production suggests new mechanistic questions for HIV-cure research (*22*). Localized lymphoid inflammation and ongoing antigen expression may contribute to reservoir persistence (*22,47,61,62*). Whether exogenous GLP-1 RAs can safely modulate these pathways or improve reservoir outcomes remains untested; their role in 'shock and kill' or 'block and lock' strategies should be considered hypothesis-generating (*22,48*). Four prospective research blueprints

Table 6. Multidimensional comparison of therapeutic strategies for weight gain and CKM syndrome in PWH

Therapeutic Strategy	Clinical Indications	Primary Molecular & Physiological Mechanisms	Distinct Immunometabolic Benefits for PWH	Core Biological Boundaries & Limitations	Evidence interpretation
GLP-1 RAs (*e.g.*, Semaglutide) (*16,17*)	Overweight/Obesity (BMI ≥ 27 kg/m^2 with comorbidities or ≥ 30 kg/m^2). CKM, MASLD under ART (*16,17*).	Central satiety and delayed gastric emptying; reductions in inflammatory biomarkers in PWH (*16,38*).	HIV-specific randomized and open-label studies show reductions in VAT and IHTG; epigenetic and gut findings remain exploratory or preliminary (*16,17,20,21*).	Gastrointestinal adverse events; lean-mass loss; weight regain after discontinuation (*59); and access/cost barriers (60*).	Randomized phase 2b evidence for body composition; other outcomes are exploratory. Grade A Recommendation (*16,17*)
Metformin (*37,47*)	T2DM. Off-label use for insulin resistance and MetD in PWH (*37*).	Hepatic AMPK activation. Mitochondrial Complex I inhibition. GDF-15 mitokine upregulation (*37*).	Low-cost therapy; HIV pilot data suggest mTOR-related reservoir effects but do not establish clinical reservoir reduction (*47*).	Negligible weight loss (<1.0 kg) (*37*). Lactic acidosis risk in advanced CKD (*37*). Vitamin B12 depletion (*37*).	Small pilot/observational evidence; not established for weight management in nondiabetic PWH. Grade B Recommendation (*37,47*)
SGLT2 inhibitors (*e.g.*, empagliflozin) (*63*)	T2DM with guideline-based cardiorenal indications (*63*).	Renal SGLT2 inhibition with glucosuria and natriuresis.	HIV-specific evidence is limited to observational use and safety; no HIV-specific cardiorenal efficacy trial was identified (*63*).	Mycotic genitourinary infections occurred in 5% versus 1% with GLP-1 agonists ($P = 0.17$); uptake was 8.8% among eligible PWH with T2DM (*63*).	Limited observational safety and utilization evidence in PWH. Grade B/C Recommendation (*39*)
Tesamorelin (*31,64*)	Targeted reduction of excess visceral abdominal fat (EVAF) in PWH with lipodystrophy (*31*).	Synthetic GHRH analog. Stimulates pituitary synthesis and release of endogenous IGF-1 (*31*).	Randomized HIV studies demonstrate selective VAT reduction without loss of subcutaneous fat (*64*).	Daily SC injection; IGF-1 elevation and glycemic monitoring; benefits diminish after discontinuation (*64*).	Randomized placebo-controlled evidence for VAT reduction in HIV-associated abdominal adiposity. Grade A Recommendation (*31*)
Lifestyle Intervention (*27*)	Universal baseline therapy for all overweight/obese PWH (*27*).	Negative caloric balance. Mechanical muscle-stretch induction. Preserves muscle mass (*27*).	Foundational nonpharmacological therapy; resistance exercise is advisable to mitigate loss of muscle mass during weight reduction (*17,27*).	Adherence can be challenging; whether lifestyle therapy reverses INSTI-associated adipose fibrosis is unknown (*29*).	Foundational therapy; HIV-specific evidence for preventing GLP-1-related lean-mass loss remains limited. Grade A Recommendation (*27*)
Bariatric Surgery (*51,52*)	Severe Class II/III obesity (BMI ≥ 35 with progressive cardiorenal collapse) (*51,52*).	Restrictive and/or malabsorptive anatomical change with endocrine and bile-acid effects.	Retrospective studies suggest acceptable short-term safety in PWH (*51,52*).	ART exposure may change after surgery; regimen-specific review and therapeutic monitoring are recommended (*53*).	Retrospective safety data; no randomized comparison in PWH. Grade B Recommendation (*51,52*)

MetD: metabolic dysfunction; SMM: skeletal muscle mass; T2DM: type 2 diabetes mellitus.

Table 7. Research-stage pharmacogenomic associations requiring clinical validation

Screening target	Genotype and reported association	Evidence status	Clinical implication
GLP1R rs10305420 (*19*)	GLP1R p. Pro7Leu effect allele associated with an additional -0.76 kg weight loss per allele; ancestry frequencies were reported (*19*).	Genome-wide association; requires external validation and prospective clinical-utility studies.	Do not alter standard semaglutide titration solely on genotype outside a research protocol.
GLP1R rs10305420 (*19*)	Absence of the GLP1R effect allele was associated with less average weight loss at the population level (*19*).	Population-level association; not a validated definition of an individual nonresponder.	Assess response using standard clinical criteria; no validated genotype-based switching threshold exists.
GIPR rs1800437 (*19*)	GIPR p. Glu354Gln variant associated with tirzepatide-related nausea or vomiting risk (*19*).	Genome-wide association; prospective validation is required.	Use product labeling and symptom-guided titration; genotype-guided dose reduction or avoidance is not validated.

Table 8. High-priority clinical trial blueprints for future HIV-metabolic research

Project Codename	Study Design & Arm Allocation	Target Study Population	Primary Scientific Hypothesis and Mechanism	Anticipated Clinical Endpoints
PRO-MUSCLE HIV	Prospective, multi-center, randomized open-label RCT: Arm A: Semaglutide + resistance training + protein; Arm B: Semaglutide monotherapy; Arm C: Lifestyle control	Sarcopenic or elderly (> 65 years) PWH on stable ART with central obesity (*27*)	Resistance exercise and high-protein intake prevent semaglutide induced lean mass loss, mitigating sarcopenia and frailty (*17,27*)	48-week change in skeletal muscle mass index (DXA); handgrip strength; Short Physical Performance Battery (SPPB) score (*17,27*)
CURE-MET HIV	Multi-center double-blind RCT: Arm A: Tirzepatide weekly (15 mg); Arm B: Semaglutide weekly (2.4 mg); Arm C: Placebo control (*16*)	Virologically suppressed PWH with high baseline inflammation (hsCRP > 3 μg/mL) (*16*)	Test whether tirzepatide or semaglutide changes inflammatory and mitochondrial-stress markers, including GDF-15, and whether those changes correlate with reservoir measures (*22,50*).	72-week change in cell-associated HIV-1 RNA/DNA ratio; Intact Proviral DNA Assay (IPDA); plasma GDF-15 level (*22,50*)
GENO-GUIDE PWH	Prospective validation study comparing standard care with a prespecified genotype-stratified research algorithm; no unvalidated dose changes outside protocol (*19*).	High-risk overweight PWH initiating GLP-1 RA therapy (*19*)	Determine whether GLP1R/GIPR variants improve prediction of response or tolerability beyond clinical factors (*19*).	12-month treatment discontinuation (dropout) rate; incidence of Grade 3/4 gastrointestinal adverse events; mean weight loss (*19*)
DUAL-MET CARDIO	Exploratory randomized trial: semaglutide plus an SGLT2 inhibitor versus semaglutide alone versus placebo (*13,39,63*).	High-cardiovascular-risk PWH with T2DM, established ASCVD, or CKD (*13,16,39*).	Test additive cardiorenal effects and safety in PWH; HIV-specific combination efficacy is not established (*13,39,63*).	96-week composite of major adverse cardiovascular events (MACE) and CKD progression; rate of genital mycotic infections (*13,16,39*)

are outlined in Table 8 (*13,16,17,19,22,27,39,50*).

4. Conclusions

GLP-1 RAs and dual co-agonists are promising options for obesity and cardiometabolic risk management in PWH. HIV-specific clinical studies support reductions in body weight, visceral adiposity, liver fat, and selected inflammatory biomarkers, while evidence for gut immune remodeling, biological-aging effects, and HIV-reservoir modification remains preliminary, exploratory, or mechanistic. Treatment should be individualized using established clinical indications, standard dose titration, resistance exercise and adequate protein intake, and long-term plans for weight maintenance. Pharmacogenomic dosing and HIV-cure applications should remain within research protocols until prospectively validated.

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