

**GLUCAGON-LIKE PEPTIDE 1 AGONISTS: SAFE AND EFFECTIVE FOR
PEOPLE WITH HIV?**

by

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Abstract

People with HIV face a higher incidence of weight gain and associated metabolic complications, largely due to antiretroviral drugs. Yet, few treatments for these conditions have been evaluated in this population. This systematic review and meta-analysis investigated the safety and efficacy of glucagon-like peptide-1 (GLP-1) receptor agonists in people with HIV. Studies were identified via PubMed and ClinicalTrials.gov, including clinical trials, observational studies, retrospective chart reviews, and case studies reporting metabolic outcomes associated with GLP-1 agonist use in people with HIV. Data were extracted and synthesized using inverse variance meta-analysis, moderator analysis, regression, and general linear modeling with bootstrapping.

Across five studies involving 567 people with HIV, GLP-1 agonists significantly improved weight, body mass index (BMI), and hemoglobin A1c, with few safety concerns. Subgroup analysis suggested semaglutide may outperform other agents, though comparative data remain limited. No significant interaction was found between GLP-1 efficacy and the use of integrase strand transfer inhibitors (INSTIs) despite concerns regarding INSTI-related weight gain. Greater weight loss was associated with higher baseline weight and BMI. Limited evidence suggested a dose-response relationship between subcutaneous GLP-1 use and metabolic outcomes. Additional data further supported positive glycemic and weight-related outcomes comparable to the general population, with no consistent evidence of immunologic or virologic compromise.

This is the first known meta-analysis of GLP-1 agonist usage in people with HIV and suggests these agents may be both safe and effective among this demographic, but with caveats. Findings support further investigation through controlled trials and real-world studies. Given

some reports of underutilization of GLP-1 agonists in HIV care, this study offers a timely contribution to research and clinical decision-making in the management of HIV-associated metabolic disease.

Dedication

This dissertation is dedicated to my father, John Edward Barnett, who was my inspiration throughout my academic journey. Despite his early departure, he had a lasting impact on who I am today. Most notably, he taught me to be resilient and persistent. In his farewell letter with his untimely passing, he told me:

“Go somewhere and be somebody. You have it in you. Please try to do what I didn’t. But most of all, do your best!!”

Completing this dissertation has been nothing more than living by those wishes.

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Pursuing an advanced degree and completing this dissertation would not have been possible without various levels of support throughout different stages of my life. The fact that I made it to this point is a miracle at best. As such, I'd like to acknowledge the many people who have provided me unwavering support before and during this specific journey: the Barnett, Fowler, Lynch, King, Faith, McDonald, and Maltese families; the long list of rugby teammates and lifelong friends I have acquired over the years (I wish I could name you all); my dogs Bella and Sailor—who have provided me with emotional support and unconditional love—one who couldn't quite make it to see this day (RIP Bella); the random but absolutely essential people who helped guide me towards a better life many years ago (e.g., Ray Gawel, Bob Higgins); my mom, Heather, for her ongoing support; and of course, my wife Nicala, who supported me as I endured uncustomary hardship, particularly in the months leading up to defense. Without each of you, as well as many I am unable to name individually, I would not have achieved this milestone.

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CHAPTER 1. INTRODUCTION

Introduction

Pharmaceutical interventions have drastically altered the landscape for various medical conditions, including immunocompromising conditions like human immunodeficiency virus (HIV) and metabolic conditions like obesity and diabetes mellitus. Most notably, these pharmaceutical interventions include the development and advancement of antiretroviral therapy (ART) for HIV (Ghosh, 2023) and glucagon-like peptide-1 (GLP-1) agonists (Gong et al., 2024). Despite these advancements, researchers have reported sparse and scattered data on the safety and efficacy of these interventions when used concomitantly (Zino et al., 2023). While GLP-1 agonists have grown in popularity in recent years, largely resulting from US Food and Drug Administration (FDA) approval for use as an obesity intervention rather than strictly for diabetes mellitus, clinicians in the US have used both ART and GLP-1 agonists for roughly 20 years (Latif et al., 2021; Moore & Chaisson, 1999; Zino et al., 2023). Despite the relatively long-term use of these drugs, limited evidence supports their concomitant use. In contrast, compounding evidence supports the increased likelihood of clinical scenarios that necessitate the use of both drugs simultaneously (e.g., ART-induced weight gain; Dupont & Yombi, 2023).

Thus, while additional clinical trials are needed to research the effectiveness and safety of these drugs, the existing data, including case reports, clinical trials, and any other studies (e.g., retrospective, observational), should be compiled and analyzed to help inform the use of these drug classes concomitantly in specific clinical scenarios. This study aimed to compile such resources and data into the first systematic review and meta-analysis on GLP-1 agonist use in people with HIV—specifically targeting those on ART—by investigating the available literature via PubMed and Clinicaltrials.gov.

Background

In 1981, HIV was discovered as a clinical condition in the US due to the emergence of acquired immunodeficiency syndrome (AIDS; Centers for Disease Control, 1982). Since then, researchers have developed a more comprehensive understanding of HIV; notably, untreated HIV elicits a prolonged and increasing presence of HIV particles in the blood (quantified as HIV RNA or HIV viral load) and a decreasing supply of CD4 T-lymphocyte (CD4) cells, which are integral to immune function. When untreated, HIV is likely to advance over time (months to years) into a more severe condition that can drastically suppress immune function, known as advanced immunosuppression or AIDS. As such, HIV RNA and CD4 cell count remained key prognostic values for people with HIV, including treated individuals (Panel on Antiretroviral Guidelines for Adults and Adolescents [Panel], 2025).

Background and Evolution of ART

In the years immediately following the discovery of HIV and AIDS, known as the pre-ART era, no available treatment suppressed the virus or protected the immune system, which led to unfavorable disease progression and high HIV-related mortality rates. For example, one study compared mortality rates in Japan before and after ART became available and found a fivefold higher rate in the pre-ART era (1986-1996; 33.6 per 1,000 person-years) compared to the late-ART era (2008–2018; 6.2 per 1,000 person-years; Tsuda et al., 2021). Another multinational study in sub-Saharan African countries showed that ART reduced mortality rates by at least 50%, even in HIV-endemic regions with fewer resources than more developed countries (Slaymaker et al., 2014).

By the mid-1980s, zidovudine (ZDV) became the first FDA-approved antiretroviral (ARV) drug, marking a pivotal moment in HIV treatment. However, monotherapy (single-drug

therapy) with ZDV proved insufficient because patients rapidly developed drug resistance (Larder et al., 1989; Rooke et al., 1989). Over time, combined ART (cART) revolutionized HIV treatment by combining different ARV drug classes, which more effectively suppressed viral replication and delayed or mitigated the risk of HIV drug resistance, as evidence showed further benefit from this approach. For example, early cART combined ZDV, a nucleoside reverse transcriptase inhibitor (NRTI), with other NRTIs such as stavudine. Early research on cART combinations with protease inhibitors (PIs), such as saquinavir, also demonstrated improved immunosuppression and fewer instances of opportunistic infections (Moore & Chaisson, 1999).

Since the development of NRTIs and PIs, researchers have established six additional ARV drug classes: non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), capsid inhibitors, CCR5 antagonists, CD4 post-attachment inhibitors, and gp120-directed attachment inhibitors (Beran et al., 2024; Goulding et al., 2024; Waters et al., 2022). Each class was designed to suppress HIV replication by disrupting a specific stage within the virus's lifecycle. For example, INSTIs inhibit the HIV enzyme integrase, preventing the virus from infiltrating a host cell's DNA and thus halting replication. PIs and NRTIs also inhibit enzymes critical to specific stages of the HIV life cycle (Saxena & Chitti, 2016; A.V. Zhao et al., 2022).

Given the continuous evolution of ARV drugs (outlined in [Table A1](#)), cART now effectively suppresses HIV in most affected people. Although ART has drastically reduced HIV-related mortality (Slaymaker et al., 2014; Tsuda et al., 2021), long-term use is associated with adverse effects, including metabolic disturbances, such as dyslipidemia, insulin resistance, and weight gain (Dupont & Yombi, 2023). These associations between ART and metabolic health

have become an important area of study, especially in populations experiencing obesity or ART-induced weight gain.

Development and Evolution of GLP-1 Agonists

Obesity and type 2 diabetes mellitus (T2DM) have reached epidemic proportions globally, with significant health and economic burdens (Di Cesare et al., 2019; Zheng et al., 2018). These conditions are characterized by insulin resistance, hyperglycemia, and chronic low-grade inflammation, contributing to cardiovascular disease, renal dysfunction, and other health complications. Traditional treatments for T2DM, such as metformin, sulfonylureas, and insulin, target glucose control but often fail to address the underlying causes of obesity and metabolic dysfunction, among other limitations (Artasensi et al., 2020; Khursheed et al., 2019). As such, metabolic biomarkers, such as HbA1c, triglycerides, and cholesterol (total cholesterol, low-density lipoproteins, high-density lipoproteins) are important indicators of metabolic health in obese individuals and those with T2DM, or both, as well as anthropometric measurements, such as total weight, body fat percentage, and body mass index (BMI).

In recent years, researchers have acknowledged GLP-1 receptor agonists as a breakthrough for the management and treatment of both obesity and T2DM. Derived from the incretin hormone GLP-1, these drugs enhance glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety (Jalleh et al., 2024). The FDA approved the first GLP-1 agonist, exenatide, in 2005, and later approved additional agents, such as liraglutide, dulaglutide, semaglutide, and tirzepatide in the following years (Latif et al., 2021). Initially, the FDA approved these drugs only for T2DM, but as recently as 2024, it expanded approvals to include clinical cases of obesity, typically defined as a BMI of at least 30 (Myerson & Paparodis, 2024). Collectively, GLP-1 agonists have demonstrated efficacy in improving

glycemic control, promoting weight loss, and reducing cardiovascular risk (Le et al., 2024; Yao et al., 2024).

Obesity and Weight Gain in People With HIV

Obesity remains an ongoing public health problem in the US, regardless of subpopulation metrics. For instance, Emmerich et al. (2024) established that over 40% of adults 20 years or older were obese between 2021 and 2023. Importantly, obesity and metabolic dysfunction are increasingly prevalent among people with HIV, largely due to the use of certain ARVs. For instance, commonly used second-generation INSTIs (dolutegravir and bictegravir) and the NRTI tenofovir alafenamide have been associated with weight gain in people with HIV (Capeau et al., 2024; Yan et al., 2024; X. Zhao et al., 2023). Importantly, despite their association with weight gain, these three ARVs are included in numerous ART regimens recommended for most people with HIV by the Panel on Antiretroviral Guidelines for Adults and Adolescents (2025), one of the leading clinical guidelines groups for HIV and AIDS worldwide. Researchers continue to investigate mechanisms for this weight gain, which may involve alterations in fat distribution (known as lipodystrophy), appetite regulation, and metabolic pathways (Chandiwana et al., 2024).

History of GLP-1 Agonists in People With HIV

Research on GLP-1 agonists in people with HIV shows promise. Early studies have explored the safety and efficacy of these drugs in managing ART-associated metabolic complications. For example, numerous studies suggest that GLP-1 agonists can reduce weight and improve glycemic control in people with HIV, similar to their effects in the general population (de Lucas et al., 2015; Eckard et al., 2024; Lake et al., 2024). Moreover, based on

preliminary data, these studies suggested that GLP-1 agonists are generally well tolerated and effective in this population.

Although early research on the concomitant use of ART and GLP-1 agonists is promising in terms of efficacy and safety, it remains limited and nascent due to the variability in ART regimens, GLP-1 agonists, patient comorbidities, and other clinical considerations. Given these limitations, this study aimed to compile existing evidence and contribute to a more comprehensive understanding of the safety and efficacy of concomitant ART–GLP-1 agonist, including specific drug combination considerations.

Problem Statement

Metabolic comorbidities, including obesity and insulin resistance, are increasing among individuals with HIV and exacerbated by some common ART regimens (Capeau et al., 2024). While GLP-1 receptor agonists are effective for weight loss and glycemic control in the general population, their safety, efficacy, and interactions with ART are unclear. This knowledge gap limits their integration into HIV care. For instance, Butale et al. (2022) reported that GLP-1 agonists were underutilized in people with HIV and speculated that the lack of use was caused by a lack of knowledge on potential drug-drug interactions.

The existing research suggests that GLP-1 agonists elicit metabolic benefits in people with HIV. For instance, Eckard et al. (2024) demonstrated reductions in both subcutaneous and visceral adiposity; despite these benefits, this study was one of only two completed clinical trials and exclusive to the GLP-1 agonist, semaglutide. As such, the overall understanding of interactions between various GLP-1 agonists and ART regimens, or components of ART regimens, is limited. Most literature consists of case studies, retrospective studies, general reviews, and expert opinions rather than high-quality trials, and no systematic reviews or meta-

analyses predated this study. Additionally, pharmacokinetic and pharmacodynamic interactions between ART and GLP-1 agonists, with data on metrics like area-under-the-curve (AUC) and maximum or minimum concentrations, are unexamined.

This study aimed to address these gaps by systematically evaluating the safety, efficacy, and drug interactions of GLP-1 receptor agonists in people with HIV.

Purpose of the Study

To evaluate the safety, efficacy, and potential drug interactions experienced by people with HIV on GLP-1 agonists, this study used a quantitative research design through a systematic review and meta-analysis, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (PRISMA, 2024). The intent of this study was to compare and analyze the effects of GLP-1 receptor agonists on individuals with HIV concurrently using ART, with a focus on determining the safety and efficacy of such combinations. Additionally, this study aimed to investigate potential differences in outcomes between specific GLP-1 agonists (e.g., semaglutide versus liraglutide) and various ART regimens, as well as to correlate treatment effects with clinical parameters, such as weight loss, glycemic control, and virologic suppression.

The study's independent variable was the use of GLP-1 receptor agonists in people with HIV (mostly those on ART), while the dependent variables were key clinical outcomes: HIV-related measures (e.g., CD4 count, HIV viral load), metabolic outcomes (e.g., BMI, weight, glycemic control via HbA1c), and safety indicators (e.g., adverse events, changes in renal and hepatic function). Covariates included patient demographics (e.g., age, sex, baseline BMI), specific ART and GLP-1 receptor agonist agents, GLP-1 treatment duration, and GLP-1 dosing. Moreover, this study systematically evaluated and quantified treatment effects across multiple

studies using statistical analyses, such as fixed-effects and random-effects models, subgroup analyses, and heterogeneity assessments based on guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2024).

Research Questions and Hypotheses

This study sought to evaluate the safety, efficacy, and pharmacological interactions of GLP-1 receptor agonists in individuals with HIV. It examined the metabolic effects of these drugs, including weight loss, glycemic control, and lipid profile changes, as well as potential interactions with ART that could alter drug metabolism, efficacy, or safety, specifically in relation to HIV RNA or CD4 cell count. This study's secondary objective was to assess whether treatment outcomes differ based on the type of ART regimen used in conjunction with GLP-1 receptor agonists. The study also investigated the incidence and severity of adverse effects associated with GLP-1 receptor agonist use in this population.

To systematically assess these questions, the study tested several hypotheses. The first hypothesis examined whether GLP-1 agonists are effective in improving metabolic outcomes in people with HIV. The null hypothesis stated that GLP-1 receptor agonists are not effective in improving metabolic outcomes (e.g., weight, BMI, glycemic control) in people with HIV and/or induce ART-related effects or underlying immunometabolic alterations. The alternative hypothesis proposed that GLP-1 receptor agonists are effective in improving metabolic outcomes in people with HIV, with results comparable to those observed in the general population.

The second hypothesis evaluated whether GLP-1 receptor agonists interact with ART in ways that impact drug metabolism, efficacy, or safety. The null hypothesis stated that no significant interactions occur, while the alternative hypothesis suggested that significant interactions do occur, potentially due to shared metabolic pathways (e.g., CYP450 enzymes,

renal clearance). A third hypothesis addressed whether the type of ART regimen influences treatment outcomes with GLP-1 receptor agonists. The null hypothesis proposed no differences across ART regimens, while the alternative hypothesis suggested that different ART regimens may interact differently with GLP-1 receptor agonists, leading to variations in efficacy or safety. Lastly, the study explored the safety profile of GLP-1 receptor agonists in individuals with HIV by assessing adverse events. The null hypothesis stated no significant difference in the incidence and severity of adverse effects in people with HIV compared to those observed in the general population, while the alternative hypothesis suggested notable variance in safety profile due to ART interactions, immune status, or other factors.

These hypotheses were tested through a systematic review and meta-analysis of available data from various clinical case studies, retrospective studies, and clinical trials using methodology outlined in [Chapter 3](#).

Theoretical/Conceptual Framework

This study utilized two complementary frameworks—the Pharmacokinetic-Pharmacodynamic (PK-PD) and the Evidence-Based Medicine (EBM)—to collectively address the safety and efficacy of ART and GLP-1 agonists when used concomitantly. These frameworks provided a strong theoretical basis for examining complex pharmacological interactions and synthesizing clinical evidence, based on real-world applications.

The PK-PD framework, introduced by Gabrielsson and Weiner (2001), focused on the relationship between drug concentrations (pharmacokinetics) and their therapeutic or adverse effects (pharmacodynamics). This theory was particularly relevant for evaluating drug interactions, such as those potentially arising from the simultaneous administration of ART and GLP-1 agonists, which could influence each other through overlapping metabolic pathways (e.g.,

CYP450 enzyme systems). This framework helped in understanding both the safety and the effectiveness of these drugs and accounted for the various drug classes and/or types of corresponding drugs (Zou et al., 2020). For instance, ART is a generalized term that refers to any combination of ARV drugs, including drugs from eight different mechanistic classes: NRTIs, NNRTIs, INSTIs, PIs, post-attachment inhibitors, CCR5 antagonists, gp-120 inhibitors, and capsid inhibitors (Azzman et al., 2024; Beran et al., 2024; Goulding et al., 2024; Waters et al., 2022). Given the inherent differences in these drugs and their mechanistic functions, this study reviewed each type in conjunction with GLP-1 agonists using the PK-PD Framework, where available.

The EBM framework, developed in the 1990s by Sackett (1997), emphasized integrating the best available clinical evidence with practitioner expertise and patient preferences. The EBM framework accounted for the research methodology and corresponding clinical data. This framework aligned with the study's goal of synthesizing scattered data to inform clinical decision-making regarding the concomitant use of these drug classes, and ideally accounted for unique clinical scenarios, such as drug-resistant HIV, presence of opportunistic infections, hepatic insufficiency (Horberg et al., 2024).

Together, these frameworks helped to bridge pharmacological science and healthcare practice to establish a more thorough evaluation of the evidence and its practical implications. Moreover, the combination of these theories provided a structured and scientifically grounded analysis of an important yet underexplored intersection in clinical pharmacology.

Nature of the Study

This study utilized a systematic review/meta-analysis methodology to address three research questions: (1) Do GLP-1 receptor agonists produce significant metabolic outcomes

(e.g., weight loss, HbA1c reduction) in people with HIV without affecting virologic response to ART? (2) Are treatment outcomes influenced by the specific ART regimen used in combination with GLP-1 therapy? (3) Is the safety profile of GLP-1 receptor agonists in people with HIV consistent with that observed in the general population? This research method was selected due to the limited availability of direct research on this topic, despite the availability of relevant data across scattered case reports, clinical trials, and observational studies (Bottanelli et al., 2024; Dardano et al., 2022; de Lucas et al., 2015; Eckard et al., 2024; Haidar et al., 2024; Lake et al., 2024; Nelson et al., 2021; Noe et al., 2024; Oriot et al., 2011; Sheffield et al., 2007). Based on fundamental scientific knowledge and a rudimentary understanding of ARTs and GLP-1 agonists, my hypotheses were: (a) the concomitant use of ART and GLP-1 agonists would be both safe and effective under *normal* (i.e., in the absence of notable comorbidities, health concerns, or biological states) circumstances, and (b) such use may warrant unique considerations or precautions in some clinical scenarios (e.g., hepatic insufficiency, pregnancy) and/or with specific combinations of ART drugs, based on the vast differences in mechanistic function and possibly drug administration route (e.g., oral, intravenous, intramuscular).

The study relied on secondary data from published literature, including both qualitative and quantitative findings sourced primarily from PubMed and ClinicalTrials.gov. The literature review included human studies involving ART *and* GLP-1 agonists, such as semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, efpeglenatide, and/or tirzepatide (Yao et al., 2024). The measurables revolved around the concomitant use of ART and GLP-1 agonists as the independent variable. The dependent variables included HIV-related outcomes (CD4 count, HIV viral load), metabolic outcomes (BMI, body fat percentage, body weight, HbA1c),

safety indicators (adverse events), and other markers of health (liver transaminases, triglycerides, or others as available).

This study utilized a structured search strategy to identify relevant studies on PubMed and ClinicalTrials.gov. Studies included were only those reporting human data, including clinical trials, case reports, or observational studies. Inclusion criteria focused on research with measurable outcomes related to efficacy and safety. Exclusion criteria were non-human studies and studies without viable safety and/or efficacy data. Collected data were systematically organized and analyzed using GraphPad Prism. Statistical evaluations included descriptive and inferential analyses, as applicable, to identify patterns, correlations, and significant findings.

Overall, this methodology was designed to synthesize existing data while addressing the research gap, providing practitioners with evidence-based insights for managing concomitant ART and GLP-1 agonist use in clinical settings.

Definitions

Given the inherent variability in previous research, this study aimed to define key parameters used within the current study. These operational definitions included the following:

- Weight loss, defined as an absolute or percent change in body weight, body fat percentage, or BMI;
- Glycemic control, defined as a reduction in HbA1c levels, expressed as absolute or percentage changes;
- Virologic suppression, defined as HIV RNA levels below 200 copies/mL and CD4 count >500 cells/mm³ in alignment with recommendations from the Panel (2025); and

- Safety, defined as the incidence of clinically significant adverse events, including but not limited to lipase elevations, transaminase changes, cardiac abnormalities, and hypersensitivity reactions.

Of note, safety underwent a subanalysis to evaluate adverse events categorized as “major” events, as well as treatment discontinuations, to better understand both the frequency and severity of adverse events.

Assumptions

This study operated under several key assumptions necessary for its meaningfulness and validity. First, it assumed that the data extracted from published studies accurately reflected the real-world clinical outcomes of patients receiving ART and GLP-1 receptor agonists. This assumption was necessary because all included studies relied on prior research methodologies, and any biases or errors in those studies could affect the conclusions drawn in this meta-analysis. Another key assumption was that variations in ART and GLP-1 receptor agonist formulations did not introduce unaccounted-for confounding variables that significantly altered patient outcomes. While subgroup analyses attempted to control for differences between treatment regimens, it was impossible to account for every potential interaction or patient-specific factor that might have influenced results (e.g., if a single patient was also taking an antipsychotic medication that was not referenced). This assumption was necessary because the available literature did not always provide detailed breakdowns of individual drug effects within combination therapies or comprehensive lists of all medications for each patient.

Unless otherwise specified, it was also assumed that adherence to treatment regimens was generally sufficient to produce meaningful clinical outcomes. Many studies reported positive adherence but did not provide granular patient-level data. In addition, evaluating the adherence

of two separate drugs on different dosing schedules could be relatively complex. Because adherence can significantly influence treatment efficacy, this assumption was pivotal when interpreting metabolic and immunologic outcomes.

Finally, it was assumed that any heterogeneity among studies could be appropriately managed through statistical techniques, such as random-effects modeling and sensitivity analyses. This assumption was necessary to ensure that pooled estimates accurately represented the broader patient population while acknowledging inherent variability in study designs, participant demographics, and follow-up durations. This was especially important given the limited availability of clinical studies in the target population.

Scope and Delimitations

This study addressed specific aspects of the research problem by focusing on the safety and efficacy of GLP-1 receptor agonists in individuals with HIV receiving ART. The review maintained internal validity by including only studies that met inclusion criteria, such as peer-reviewed publications, with clearly defined methodologies and documented safety and/or efficacy outcomes in people with HIV using GLP-1 agonists. This study relied on previously published studies with established methodologies to minimize selection bias and confounding variables, although the variety of studies included—due to the general lack of available clinical literature—could influence the outcomes of this study.

The study's boundaries were defined by its focus on adults with HIV who are concurrently using ART and GLP-1 receptor agonists. Pediatric populations, pregnant individuals, and those with significant comorbid conditions unrelated to HIV or metabolic health were typically excluded to maintain homogeneity and relevance, based on exclusion criteria in prior studies. Additionally, studies that did not explicitly report safety or efficacy outcomes or

lacked sufficient data for meta-analysis were also excluded. While this approach improved internal validity, it limited external validity by excluding certain populations that might have also benefited from these therapies and that would be evaluated in future research.

Regarding theoretical and conceptual frameworks, this study did not investigate broader metabolic theories or immunological mechanisms beyond their direct relevance to the research question. The study also does not evaluate nonpharmacologic interventions, such as dietary changes or exercise, which might have influenced metabolic outcomes in this population (Puerto Valencia et al., 2024). These exclusions helped maintain a focused scope but also highlighted areas for future research.

The generalizability of this study was subject to certain constraints. Given that this review relied on data from published research, findings were inherently limited to the characteristics of the included study populations and measured outcomes. Variability in study designs, sample sizes, and ART/GLP-1 regimens might have affected the applicability of results to broader clinical settings. However, by incorporating a multitude of studies from different regions and healthcare settings, the meta-analysis aimed to produce findings relevant to various populations.

Limitations

This study had several limitations related to design and methodological constraints. One primary limitation was the reliance on secondary data, which restricted control over data quality and consistency across studies (Olabode et al., 2019). Differences in study methodologies, sample sizes, and population characteristics might have introduced variability that cannot be fully accounted for, potentially affecting the accuracy of pooled estimates. Additionally, the lack of randomized controlled trials in this area limited the ability to establish causality, as

observational studies might have contained confounding variables that influence reported outcomes.

Study selection and reporting biases also posed potential threats to validity. Meta-analyses recognized publication bias as a concern, since studies with significant findings were more likely to be published than those with null results (Muff et al., 2022). To mitigate this issue, this study aimed to use funnel plots and Egger's tests to assess and adjust for publication bias where possible (Higgins et al., 2024). Additionally, the inclusion criteria might have introduced selection bias by prioritizing peer-reviewed studies with available data; however, this approach helped to ensure methodological rigor and reliability.

To address these limitations, this study applied multiple analytical strategies, including sensitivity analyses and heterogeneity assessments, to evaluate the comprehensiveness of any statistical findings. The analysis used random-effects modeling to account for variations across studies and performed subgroup analyses to explore potential differences in treatment effects. Despite these challenges, this systematic review and meta-analysis aimed to provide a balanced and comprehensive synthesis of existing evidence to inform clinical practice and future research.

Significance

This study contributed to the existing body of knowledge by providing a comprehensive synthesis of available data on the concomitant use of GLP-1 receptor agonists and ART in individuals with HIV. Given the limited research in this area, the findings of this systematic review and meta-analysis helped bridge gaps in understanding the metabolic and virologic effects of these combined therapies. The results also informed future clinical trials and guided the development of best practices for managing weight and glycemic control in individuals with HIV. Ultimately, this information helped improve knowledge and confidence in prescribing

these drugs concomitantly to increase their utilization when necessary, supporting concerns of drug underutilization noted by Butale et al. (2022).

From a practical standpoint, this study had implications for both clinical practice and healthcare policy. Clinicians benefited from evidence-based insights into the safety and efficacy of GLP-1 receptor agonists in patients with HIV, which might influence prescribing practices and patient monitoring strategies. Additionally, policymakers and healthcare systems can use these findings to develop guidelines for integrating GLP-1 receptor agonists into HIV care, particularly for patients experiencing ART-associated metabolic complications. This could have included presumptive prescriptions to help mitigate the risk of ART-induced weight gain before it occurs.

This study also had broader implications for positive social change by promoting more effective management strategies for metabolic health in individuals with HIV. Given the increasing prevalence of obesity and metabolic disorders in this population, improved treatment strategies could enhance quality of life, reduce the burden of comorbid conditions, and contribute to more equitable healthcare outcomes. Importantly, while weight gain was the direct focus of GLP-1 agonists, increased weight and adiposity had well-documented associations with other comorbidities, including cardiovascular disease (Powell-Wiley et al., 2021). This study ultimately aimed to help optimize long-term health outcomes for people living with HIV while simultaneously addressing the intersection of infectious disease management and chronic disease prevention.

Summary

This study conducted a systematic review to assess the safety and effectiveness of concomitant ART and GLP-1 agonist administration by compiling data from clinical trials, case

reports, and observational studies. It addressed a major gap in knowledge and confidence surrounding the concomitant use of these drugs by synthesizing existing evidence to better understand their safety and efficacy from multiple clinical perspectives (e.g., for HIV treatment and for metabolic function). This was especially relevant for individuals who were obese or experiencing ART-induced weight gain. This research aligned with my DHSc degree, as it merged clinical pharmacology with evidence-based practice to guide therapeutic decisions in complex, multidisciplinary settings.

CHAPTER 2. LITERATURE REVIEW

Introduction

Researchers have studied and analyzed ART and GLP-1 agonists for over two decades. Yet, the concomitant use of these drugs has remained relatively understudied, despite known concerns regarding scenarios in which their concomitant use was clinically appropriate (e.g., people with HIV who experience weight gain; Dupont & Yombi, 2023). As such, it was important to understand the effects of these drugs when used concurrently. This chapter reviews the available literature to disseminate the fundamentals of both drug types.

Literature Search Strategy

The literature review for the current study used both PubMed and ClinicalTrials.gov as primary search engines to identify relevant studies and clinical trials. The approach involved specific search terms, inclusion and exclusion criteria, and a systematic analysis of identified literature to ensure the focus remained on relevant findings, especially considering that GLP-1—while targeted by advantageous pharmaceutical drugs in modern times—has been researched as a naturally occurring biomarker in historical research (Jędrysik et al., 2024).

Search Methodology

The review identified PubMed and ClinicalTrials.gov as the most appropriate platforms due to their extensive repositories of biomedical and clinical research. PubMed provided access to peer-reviewed studies, while ClinicalTrials.gov offered insights into ongoing, completed, and terminated clinical trials.

The PubMed search query used Boolean operators to maximize the capture of relevant studies: (“HIV” OR “human immunodeficiency virus” OR “antiretroviral”) AND (“glucagon-like peptide” OR “semaglutide” OR “liraglutide” OR “dulaglutide” OR “exenatide” OR

“lixisenatide” OR “albiglutide” OR “efpeglenatide” OR “tirzepatide”). For ClinicalTrials.gov, the search parameters were tailored to align with its interface, focusing on “human immunodeficiency virus” as the “Condition/Disease” and using the same terms as in the PubMed query as the “Intervention/Treatment.”

The review included studies only if they explicitly referenced the application of GLP-1 receptor agonists in humans with HIV. Studies were excluded if they: focused on animal models without human applicability; addressed natural GLP-1 alterations without discussing pharmacological interventions; or did not directly investigate the use of GLP-1 receptor agonists. The study manually reviewed all identified literature for relevance and alignment with these criteria.

The initial search on PubMed identified 42 studies. The search deemed 24 studies relevant for further analysis after applying inclusion and exclusion criteria. The retained studies covered various aspects of GLP-1 receptor agonists’ pharmacological effects, their potential benefits in metabolic and inflammatory complications, and their specific applicability in HIV-positive populations.

The search on ClinicalTrials.gov identified eight clinical trials, of which seven met the inclusion criteria. These trials provided information on the design, intervention, and preliminary outcomes of GLP-1 receptor agonist applications in HIV care.

Scope of Literature Review

The review included all historical studies in the initial PubMed literature review, ultimately spanning 2005 to 2024. However, applying the exclusion criteria narrowed the final set of studies to those published between 2007 and 2024. Similarly, all historical clinical trials identified on ClinicalTrials.gov were reviewed, spanning from 2005 to 2024, based on their

“First Posted” date upon initial review. Applying the exclusion criteria limited the included clinical trials to those between 2013 and 2024.

Types of Literature and Sources

The literature review primarily included peer-reviewed journal articles accessed through PubMed and clinical trial records obtained from ClinicalTrials.gov. The PubMed publications appeared in numerous formats (e.g., case studies, randomized controlled trials, reviews), as shown in [Table A2](#).

Given the clinical nature of this research and the regulations that often limit comprehensive studies for safety reasons, the review considered all applicable studies to enhance the total body of research. In this case, defining seminal works and foundational studies proved challenging to define, as recent studies often served as the first legitimate and exclusive clinical trials involving the targeted population (people with HIV using GLP-1 agonists). For instance, from 2007 to 2023, researchers developed only 11 studies that fulfilled the inclusion criteria, while 13 such studies emerged in 2024 alone. Similarly, at the time of this study, only one RCT on the target population had been completed; all others were terminated, recruiting, or incomplete. As such, this study included all available and applicable studies to support the growing body of research. These limitations in available research prompted a review of multiple databases (i.e., PubMed and ClinicalTrials.gov).

Theoretical Foundations

This study is grounded in two complementary frameworks: the Pharmacokinetic-Pharmacodynamic (PK-PD) framework and the EBM framework. These frameworks collectively provided a simple yet thorough theoretical foundation for evaluating the safety and efficacy of ART and GLP-1 receptor agonists when used concomitantly. These frameworks worked

collaboratively to integrate pharmacological science and the synthesis of clinical evidence to address the complex interactions between these drug classes and their implications on patient care. Considering the ongoing concerns of weight gain in people with HIV, both ART-induced and non-ART-related, these frameworks helped provide insights into a promising avenue for weight management with a relatively high-risk population.

The Pharmacokinetic-Pharmacodynamic Framework

Gabrielsson and Weiner (2001) introduced the PK-PD framework to examine the relationship between drug concentrations (pharmacokinetics) and their corresponding therapeutic or adverse effects (pharmacodynamics). This framework evaluated how the body absorbed, distributed, metabolized, and excreted drugs, and how these processes influenced drug action and interaction. The PK-PD framework was particularly relevant for navigating drug-drug interactions, such as those that arose from the concurrent administration of ART and GLP-1 receptor agonists.

A key proposition of the PK-PD framework was the recognition that overlapping metabolic pathways influenced drug efficacy and safety. For instance, ART comprised various drug classes—including NRTIs, NNRTIs, INSTIs, and PIs—each with unique pharmacokinetic profiles. Many drugs across these ARV classes rely on cytochrome P450 (CYP450) enzymes and demonstrate altered drug metabolism when used concomitantly with other drugs that induce or inhibit the same enzyme(s). For instance, the PIs ritonavir and darunavir have been shown to inhibit CYP3A4 and interact with drugs such as anticonvulsants like carbamazepine and selective serotonin reuptake inhibitors (SSRIs; Stolbach et al., 2015). Such interactions often cause drug concentrations to increase or decrease to levels that render the drugs either ineffective or unsafe. While GLP-1 agonists have typically exerted minimal effects on CYP450 enzymes—

due to their different metabolic and excretory mechanisms—questions remained about their safety and effectiveness due to unique demographic factors (e.g., altered GLP-1 function in obese persons), renal function impacts, and slowed gastric motility (Calvarysky et al., 2025; Gutierrez et al., 2019; Kvitne et al., 2022; Tuan et al., 2024).

Researchers have relied on the PK-PD framework to evaluate drug interactions, dose-response relationships, and individualized pharmacotherapy. Previous studies have used this framework to investigate the safety and efficacy of ART in combination with other drugs in populations with comorbidities, such as those with diabetes and cardiovascular disease, including statin therapy among people with HIV (Gilbert et al., 2016; Ramirez et al., 2024). Similarly, this framework has been used to review the concomitant use of GLP-1 agonists and other drug classes, including hormones (e.g., levothyroxine) and antipsychotics (Buzea et al., 2022; Calvarysky et al., 2024; Hauge et al., 2019). These applications demonstrated the framework's utility in examining the pharmacological compatibility of complex drug regimens.

The EBM Framework

In the 1990s, Sackett (1997) conceptualized the EBM framework to emphasize integrating the best available clinical evidence (generally data-driven) with practitioner expertise and patient preferences. This framework advocated for a systematic approach to clinical decision-making, prioritizing rigorously obtained evidence to guide therapeutic interventions (Djulfbegovic & Guyatt, 2017).

The EBM framework has been centered on the idea that clinical decisions should be informed by a hierarchy of evidence, ranging from randomized controlled trials (RCTs) to observational studies and expert opinions. It also recognized the importance of tailoring therapeutic strategies to individual patient circumstances, such as drug-resistant HIV, coexisting

conditions, and metabolic alterations. Moreover, the framework accounted for subjective variables like patient preferences, when applicable (Borgerson, 2009; Engle et al., 2021; Woolf, 1999).

Researchers have extensively applied the EBM framework to evaluate ART regimens, focusing on efficacy, safety, and adherence in diverse populations, including people with HIV with drug-resistant HIV, opportunistic infections, and hepatic insufficiency (Horberg et al., 2024). The EBM framework guided the evolution of ARVs (see [Table A1](#)), promoting the development of more effective treatment options with fewer adverse effects, such as the development of second-generation INSTIs (Smith et al., 2021; A.V. Zhao et al., 2022). Similarly, researchers have used the EBM framework to assess the role of GLP-1 receptor agonists in managing metabolic disorders, providing insights into their effectiveness in real-world settings. Given the evidence supporting the effectiveness and overall safety of GLP-1 agonists for T2DM—especially considering the positive influence and risk reduction on metabolic-related comorbidities—these drugs gained enough clinical support over the years to receive FDA approval for the treatment of obesity, exemplifying the influence and scope of the EBM framework (Knudsen, 2024; Myerson & Paparodis, 2024).

The integration of the PK-PD and EBM frameworks provided a comprehensive foundation to address the research questions at hand. Simply, the PK-PD framework outlined the mechanistic basis of potential drug interactions, whereas the EBM framework contextualized these findings within the broader landscape of clinical evidence via efficacy/outcome data that directed clinicians to use the safest and most practical interventions or treatments. These frameworks collectively supported a rigorous evaluation of the safety and efficacy of ART and GLP-1 receptor agonists, based on the available clinical evidence to date.

Conceptual Framework

The current study anchored its conceptual framework in the overarching concept of pharmacological safety and efficacy within HIV treatment and management, based on the multifaceted applications of concomitant ART (for the treatment of HIV) and GLP-1 agonists (for the management of obesity, diabetes, or ART-related weight gain). As previously referenced, the study integrated two established paradigms—the PK-PD framework and the EBM framework—to evaluate drug interactions and clinical evidence, with the primary goal to understand the practicality of concurrent drug use among individuals living with HIV.

Definition of the Concept

Pharmacological safety and efficacy refer to the ability of therapeutic agents to achieve desired clinical outcomes while minimizing adverse effects. In HIV treatment, ART effectively suppresses viral replication, typically measured by HIV RNA (also known as HIV viral load) and considered successful at <200 copies/mL (Foka & Mufhandu, 2023; Panel, 2025). CD4 cell count also serves as an important metric of treatment efficacy, though the threshold of CD4 count success varies slightly based on the time since ART initiation, with the ultimate goal of immune reconstitution, achieving a CD4 cell count of >500 cells/mm³ (Panel, 2025). GLP-1 agonists treat metabolic comorbidities, such as T2DM and obesity, and their success depends on the clinical indication. For example, patients with T2DM should achieve HbA1c levels between 7% and 8% to consider GLP-1 agonist therapy fully effective (Qaseem et al., 2018). In contrast, when GLP-1 agonists are used to support weight loss, a sustained loss of at least 5% total body weight is often used as a threshold for success (Manne-Goehler et al., 2025). Because some ARVs have been associated with weight gain, using GLP-1 agonists for metabolic comorbidities

(e.g., diabetes, obesity) requires thorough evaluation of pharmacokinetic and pharmacodynamic interactions to confirm ongoing effectiveness and safety for multiple clinical indications.

Researchers have found the PK-PD framework to be instrumental in analyzing drug interactions by modeling the relationships between drug concentrations, therapeutic effects, and adverse outcomes. Generally, drug concentrations are evaluated via parameters, such as area under the curve (AUC), maximal concentration ($C_{\max}$), half-life ($t_{1/2}$), and clearance (Du et al., 2019; Yang & Yang, 2024). Such parameters provide context for both drug effectiveness and safety. Therapeutic effects generally measure intended outcomes related to drug effectiveness, such as the aforementioned viral suppression for ARVs and reductions in HbA1c or total body weight for GLP-1 agonists. Lastly, adverse outcomes refer to unintended and/or undesirable effects of drugs, which vary widely in severity (e.g., gastrointestinal discomfort, hypersensitivity reactions, sudden cardiac arrest). Thus, the PK-PD framework applies to HIV care as evidenced by the identification of metabolic pathways, such as the cytochrome P450 enzyme system, in mediating drug-drug interactions for many of these drugs (Stolbach et al., 2015).

On the other hand, the EBM framework more so emphasizes the integration of clinical evidence, practitioner expertise, and patient preferences to guide therapeutic decision-making. Researchers have applied this framework extensively in HIV research to evaluate the effectiveness and safety of ART regimens. For instance, while evidence supports the use of many ART regimens, some regimens may have limitations that affect treatment adherence (ultimately affecting drug effectiveness), such as pill size, pill count, and dosing frequency. As such, many patients prefer single-tablet once-daily ART regimens to simplify such variables (Degroote et al., 2022; Paoli et al., 2024). Thus, the EBM framework accounts for the entirety of the treatment

experience and can be particularly valuable in complex clinical scenarios (e.g., drug resistance, coexisting infections, adverse drug effects).

Key Statements and Definitions

Within the PK-PD framework, key concepts refer to those mechanisms that govern drug behavior and effects. The therapeutic window, for instance, refers to the range of drug concentrations within which a therapeutic effect is achieved without significant toxicity (Fang et al., 2024). Another essential concept is metabolic pathway interaction (or drug-drug interactions), which refers to the potential for co-administered drugs to compete for or inhibit common metabolic enzymes (Manubolu, 2024). Such interactions can significantly affect drug clearance and bioavailability, which resultantly influence dosing and safety.

Similarly, the EBM framework incorporates foundational principles that guide evidence-based clinical practices. The hierarchy of evidence refers to the prioritization of data from RCTs and systematic reviews (ideally based on RCTs) as the gold standard for informing clinical decisions. Moreover, the hierarchy of evidence includes data and insights from other study formats (e.g., observational studies, retrospective studies) and expert opinions, but to a lesser degree (George et al., 2021). Additionally, patient-centered care refers to the consideration of individual patient characteristics, preferences, and circumstances in the application of clinical evidence, ensuring that treatments are both scientifically valid and tailored to the needs of the individual, as exemplified previously with the general preference towards single-tablet, once-daily ART regimens. These principles collectively support the integration of robust data and personalized care in clinical decision-making.

Historically, researchers have applied the PK-PD framework to evaluate ART drug interactions, aiming to optimize dosing regimens and minimize adverse effects. For instance, the

Panel of Antiretroviral Agents in Adults and Adolescents With HIV (2025) provides an overview of known drug-drug interactions, including associated dosing changes, contraindications, or other considerations. Similarly, researchers have used the EBM framework to guide systematic reviews and meta-analyses on ART efficacy, informing clinical guidelines for managing HIV in a multitude of specific populations and unique scenarios, including pregnant people, first-line treatment failure, and people with substance use concerns (Hoffmann et al., 2023; Kane et al., 2022; Shinar et al., 2022).

This study built upon these frameworks to better understand the safety and efficacy of co-administering GLP-1 receptor agonists with ART in people living with HIV. The PK-PD framework facilitated an understanding of the mechanistic basis for potential drug-drug interactions, while the EBM framework supported the synthesis of clinical evidence to inform best practices. By integrating these frameworks, the study supported a critical gap in the literature by compiling the existing, albeit limited, evidence involving this unique demographic.

Literature Review Related to Key Variables and/or Concepts

As [Table A2](#) shows, the availability of literature formally investigating the concomitant use of ARVs and GLP-1 agonists was limited. This literature review on the use of GLP-1 receptor agonists in individuals with HIV highlights a nascent field of study with research primarily emerging within the past two years (2023 and 2024), despite technically originating nearly two decades ago. The hierarchy of evidence, as outlined by the EBM framework, largely consists of lower-tier evidence (e.g., general reviews and expert opinions) with fewer higher-tier studies (e.g., RCTs). Notably, no systematic review or meta-analysis has collectively evaluated the existing studies on concomitant ART and GLP-1 agonist use, which highlights a significant gap in the literature and an opportunity to shift the paradigm within the hierarchy of evidence to

be more authoritative. Given that the majority of published studies were conducted in recent years, this section is organized into hierarchical tiers of evidence. This literature review focuses on the safety and efficacy of both drug classes using the following dependent variables (as available):

- **HIV-related outcomes:** CD4 count, HIV viral load.
- **Metabolic outcomes:** BMI, body fat percentage, body weight.
- **Safety indicators:** Adverse events, including major events.

Of note, additional parameters that may indicate potential treatment concerns, such as renal function (via eGFR) and hepatic function (via liver transaminases), are referenced if applicable data suggest a potential association.

Reviews and Expert Opinions

Much of the available literature on combined ART and GLP-1 agonist use consisted of reviews and expert opinions. Of 24 total eligible publications, nine (37.5%) were classified as low-tier evidence, based predominantly on general reviews and expert opinions. These publications included reviews (7), editorials (1), and news articles (1) (Culha et al., 2016; Hwang et al., 2024; Lee & Capeau, 2024; Lenharo, 2024; Parra-Rodriguez & O'Halloran, 2023; Patoulis et al., 2024; Sarkar & Brown, 2024; Thomas & Srinivasa, 2024; Zino et al., 2023). These sources generally emphasized the potential and/or witnessed benefits of GLP-1 agonists for weight management, metabolic health, and glycemic control in individuals with HIV.

Overall, the publications in this hierarchical tier agreed that GLP-1 agonists had legitimate potential to provide positive outcomes in weight management for people with HIV on ART (Culha et al., 2016; Hwang et al., 2024; Lee & Capeau, 2024; Lenharo, 2024; Parra-Rodriguez & O'Halloran, 2023; Patoulis et al., 2024; Sarkar & Brown, 2024; Thomas &

Srinivasa, 2024; Zino et al., 2023). Most recently, Thomas and Srinivasa (2024) provided an overview of GLP-1 agonist research on people with HIV, but their study lacked a detailed data analysis specific to ART regimens or patient subpopulations. Collectively, these works suggested early optimism while consistently calling for more robust, higher-quality research in the target population.

The general consensus was straightforward on the potential benefits of the concomitant use of ARVs and GLP-1 agonists; however, some unique and situation-specific outcomes were noteworthy. For instance, Lee and Capeau (2024) referenced that GLP-1 agonists may be more appropriate for individuals with predominantly subcutaneous fat accumulation, whereas those with predominantly visceral fat accumulation may benefit more from tesamorelin. Moreover, the authors referenced the positive therapeutic effects of GLP-1 agonists, namely semaglutide, on people with HIV using an INSTI-based regimen. Similarly, Parra-Rodriguez and O'Halloran (2023) noted the positive influence of GLP-1 agonists on people with HIV using modern ART regimens with weight gain, including INSTIs and tenofovir alafenamide, a common NRTI.

Early evidence and experts generally favor the use of GLP-1 agonists, but concerns remain. For instance, Zino et al. (2023) highlighted the therapeutic potential of the GLP-1 agonists liraglutide and semaglutide while addressing concerns about drug interactions and monitoring requirements. Specifically, this study highlighted the success of GLP-1 in weight loss and glycemic control but cautioned about potential concerns with heart rate variability in people with HIV using PI-based regimens. Moreover, Zino et al. (2023) referenced recommended additional monitoring when used with atazanavir- and rilpivirine-based ART regimens due to absorption concerns caused by alterations in gastric pH.

While the early expert consensus suggested that combined ARV and GLP-1 agonist use was generally safe and efficacious—largely due to the differences in metabolic pathways—the optimal dosing of these drugs may still require further monitoring. According to Hwang et al. (2024), most applicable data on semaglutide use in people with HIV was conducted with a 1.0 mg per week dose (injected), aligning with the maximum approved by the FDA at the time of the study. Yet, the lawful injectable semaglutide doses have increased to 2.4 mg (at least in the US), likely due to its demonstrated efficacy and added clinical indications as an anti-obesity drug (Amaro et al., 2022). Additionally, the dosing may differ for other similar but non-identical GLP-1 agonists, drawing further speculation on the otherwise-positive outcomes thus far (Hwang et al., 2024).

Case Studies

Five case studies from 2007 to 2022 provided valuable insights into individual clinical experiences with GLP-1 agonists. These reports highlighted improvements in weight loss, glycemic control, and lipid profiles in people with HIV who were treated for metabolic conditions with GLP-1 agonists, including dulaglutide, exenatide, and liraglutide. Sheffield et al. (2007) noted the first legitimate research on the use of GLP-1 agonists in people with HIV, using exenatide off-label for a 40-year-old obese patient with insulin-resistant type 1 diabetes mellitus who also had HIV. This case reported that the patient experienced increased weight and insulin resistance after initiating ART. Yet, this patient experienced significant weight loss (nearly 20% of total body weight) alongside notable reductions in HbA1c while continuing to take an ART regimen of efavirenz (EFV)/tenofovir (TFV)/lamivudine (3TC) over the course of nearly a year. A few years later, Oriot et al. (2011) demonstrated that exenatide elicited similar positive benefits in a 47-year-old patient with type 2 diabetes and HIV. Over the course of 14 months,

this patient experienced significant improvements in body fat percentage (decreased by 5.5%), beta-cell secretion (increased by 28%), and HbA1c (decreased by 1.9%; Oriot et al., 2011). In this case, the patient used EFV/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), showing similarities with that of Sheffield et al. (2007). The two case studies provided a small sample supporting the use of exenatide and an NNRTI plus two NRTI ART regimen (see [Table A1](#) for reference to drug classes).

The FDA approved liraglutide treatment for type 2 diabetes in 2010, five years after it approved exenatide in 2005. Shortly thereafter, Diamant and van Agtmael (2012) reported the first official case study on a type 2 diabetic with HIV using liraglutide. This 57-year-old patient had uncontrolled diabetes despite insulin treatment. Similar to previous cases involving exenatide, the patient experienced significant improvements in body weight (a reduction of up to 14kg, ~12% of total body weight), as well as improvements in lipid profile (triglycerides, cholesterol) and liver enzymes over four months. Importantly, HIV RNA remained undetectable throughout the observation period. Although some regimen changes occurred, this patient completed most of the intervention using raltegravir (RAL)/TFV/3TC, marking the first evidence supporting an INSTI-based ART regimen (Diamant and van Agtmael, 2012). Several years later, de Lucas et al. (2015) detailed similarly significant metabolic improvements, including body weight, lipid profile, and fasting glucose, in a 62-year-old male with HIV and type 2 diabetes following liraglutide treatment while taking RAL/TFV/3TC. However, the authors did not report HIV RNA data. Of note, due to the improvements in metabolic parameters and function, the patient's medication doses (metformin and Levemir) were reduced at or before 24 weeks (de Lucas et al., 2015).

The FDA approved dulaglutide for the treatment of T2DM after both exenatide and liraglutide. In 2022, Dardano et al. (2022) noted the positive effects of dulaglutide on a 55-year-old diabetic woman with HIV who recently overcame sepsis. In that case, dulaglutide use was associated with improved glycemic control, mild weight loss, and improvements in various biomarkers (e.g., creatinine). At the patient's follow-up, pre-existing liver steatosis had resolved, and the patient exhibited no adverse effects related to renal or hepatic function. The patient received an ART regimen consisting of bictegravir (BIC)/FTC/tenofovir alafenamide (TAF), marking the first reported case using a second-generation INSTI (BIC) (Dardano et al., 2022).

Retrospective Cohort Studies

Six retrospective cohort studies offered broader, population-based perspectives on GLP-1 agonist use in individuals with HIV. For example, the first published observational cohort study evaluated people with type 2 diabetes from January 2018 through July 2019, noting 17 patients with HIV (Nelson et al., 2021). This study was rudimentary in the sense that it did not precisely evaluate the influence of GLP-1 agonists on people with HIV; rather, it investigated the likelihood that type 2 diabetes with HIV would need such treatment. Importantly, this study also permitted, and did not provide differentiated data for, SGLT-2 prescription as an alternative to GLP-1 agonists when indicated. While the sample size was limited and participants without HIV outnumbered those with HIV more than three to one, researchers observed no statistically significant difference in glycemic control between the groups. Both groups demonstrated improvements in glycemic control, as indicated by three-month HbA1c reductions, regardless of whether they initiated GLP-1 agonist or SGLT-2 therapy. Of note, 35% of people with HIV were started on antidiabetic medication compared to only 18% of those without HIV, demonstrating that routine interventions may be less effective and warrant the use of GLP-1 agonists, or both, in

this demographic. Otherwise, no specific data were reported on ARV regimens (Nelson et al., 2021). In a similar capacity, a 2022 retrospective cohort study analyzed the medical history of 262 patients with HIV to evaluate the use of SGLT-2/GLP-1 agonist use in this population (Butale et al., 2022). Of the 35 patients identified with HIV and diabetes, only 5 (14.3%) received GLP-1 agonists for diabetes treatment, despite clear and statistically significant differences in metabolic parameters. The authors speculated that the low rate of use was related to a lack of available literature supporting its use in this demographic, particularly due to concern over potential drug interactions (Butale et al., 2022).

In 2023, Bottanelli et al. (2023) developed a small retrospective study of 15 ART-experienced (at least one year) people with HIV treated with GLP-1 agonists for type 2 diabetes. Of those evaluated, three, five, and seven patients received semaglutide, liraglutide, and dulaglutide, respectively. Patient ART regimens included three with PIs, five with INSTIs, five with NNRTIs, and two with both INSTIs and NNRTIs. The exact distribution of combined GLP-1 agonists and ART regimens among patients remained unclear (e.g., dulaglutide with an INSTI regimen; Bottanelli et al., 2023). Overall, this study demonstrated a relatively modest effect on weight loss, considered statistically insignificant at 24 months, although the authors speculated that such outcomes may be related to the relatively high utilization of dulaglutide over semaglutide and liraglutide. Moreover, researchers did not report HIV viral load after baseline to validate that all patients maintained previously achieved virologic suppression (Bottanelli et al., 2023).

In 2024, three additional observational cohort studies were published on people with HIV who used GLP-1 agonists. An early and relatively small retrospective study analyzed data from 70 people with HIV on GLP-1 agonists, with 33 and 37 on dulaglutide and semaglutide,

respectively. This study aimed to evaluate the safety of GLP-1 agonists in people with HIV based on immunologic alterations and reported a relatively small but statistically significant decrease in CD4 cell count after GLP-1 agonist administration ($p < .05$), with noted interindividual variability in CD4 cell count fluctuations (Noe et al., 2024). While such decreases may not be clinically significant for some people with HIV, they may warrant additional monitoring and/or avoidance of GLP-1 agonists in certain people with HIV (e.g., those with virologic failure) if future data support these trends.

In one study that reviewed patient data from 2018 to 2022, 222 eligible patient files were reviewed, with reported weight loss averaging 6.47 kilograms and HbA1c reductions of 1.07% at one year following semaglutide administration (Haidar et al., 2024). Most participants were on an ART regimen that included an INSTI (82.4%) or TAF (69.4%)—ARVs commonly associated with weight gain—yet weight loss remained statistically significant regardless of ART regimen ($p < .001$). While the study evaluated baseline HIV viral load and CD4 cell count, these values were not reported after semaglutide intervention (Haidar et al., 2024). A final retrospective single-center cohort study reciprocated similar outcomes in 225 people with HIV receiving various GLP-1 agonist interventions (Nguyen et al., 2024). In addition, this study noted that greater weight loss (e.g., $> 5\%$ body weight) was associated with longer GLP-1 agonist use, higher initial BMI, and for tirzepatide-specific interventions. Thus, while all GLP-1 agonists analyzed (dulaglutide, exenatide, liraglutide, semaglutide, tirzepatide) resulted in weight loss, tirzepatide appeared to be the most effective. Interestingly, the study data reinforced Bottanelli et al.'s (2023) speculation that dulaglutide was associated with a less substantial effect, as 71% of those using dulaglutide failed to achieve more than 5% weight loss, compared to 48.3% of those using injectable semaglutide. The ART regimen did not appear to have any substantial effect on

weight loss outcomes. And like most previous studies, the researchers reported only baseline HIV viral load and CD4 count (Nguyen et al., 2024).

Clinical Trials

Clinical trials yielded valuable outcome data from interventions in controlled settings and helped clarify the scope of potential outcomes. Although RCTs are often considered the gold standard of evidence, they remain scarce in this field. As of 2024, researchers had completed only two clinical trials (one RCT) on people with HIV using GLP-1 agonists. A third clinical trial appeared in the literature search and targeted the intended population, but was incomplete and focused on evaluating informed consent quality rather than clinical outcomes (O’Sullivan et al., 2022).

One of the two primary clinical trials was a Phase 2b double-blind, placebo-controlled single-center RCT (Eckard et al., 2024). This 32-week study evaluated 108 people with HIV who used semaglutide (54 received intervention, 54 received placebo) for HIV-related lipohypertrophy. This study aligned with previous observational research and demonstrated significant decreases in fat mass, both total and abdominal (subcutaneous and visceral). Importantly, this study noted no statistically significant differences between groups for adverse effects, though the study noted three notable adverse events—grade 4 elevated lipase and two cases of cholelithiasis. Additionally, study data suggested that INSTI-based ART regimens may be associated with mild lipase elevations (Eckard et al., 2023). All intervention participants maintained HIV-1 RNA <400 copies/mL, though this value was considerably higher than many experts used to define virologic suppression (e.g., 50 copies/mL or 200 copies/mL). The study provided some ART regimen data, noting 88 (81%) on an INSTI, 18 (17%) on a PI, 79 (73%) on TAF, and 66 (61%) on both an INSTI and TAF, it reported no regimen-specific data to better

understand the exact doses, formulations, and/or brands used within the semaglutide group (Eckard et al., 2024).

The remaining clinical trial was Lake et al.'s (2024) open-label single-arm trial known as the SLIM LIVER trial, which analyzed metabolic changes in HIV-related steatotic liver disease with semaglutide for 24 weeks. This Phase 2b RCT study evaluated data from 49 participants (51 originally included) and established clinically and statistically significant reductions in intrahepatic triglycerides (liver fat), metabolic dysfunction-associated steatotic liver disease (MASLD) status, and numerous metabolic parameters (e.g., HbA1c, triglycerides, cholesterol; Lake et al., 2024). In this study, three (6.1%) of the 49 participants started the semaglutide intervention with HIV RNA <50 copies/mL, but exceeded that threshold by Week 24. Researchers could not determine the magnitude and cause of the HIV RNA increases. They observed no statistically significant changes in CD4 cell count based on the available data. Like Eckard et al. (2024), the study reported ARV drug class data, noting that participants on regimens including INSTIs (n = 40, 82%), NNRTIs (n = 10, 22%), and PIs (n = 2, 4%), but did not specify regimen details. A subanalysis of the SLIM LIVER study further evaluated weight loss and muscle function of 46 participants. This subanalysis found that muscle volume was significantly decreased ($p < .001$), but muscle function did not decline and may be slightly improved based on multiple performance tests (Ditzenberger et al., 2024).

Aside from the trials referenced above, each identified via PubMed literature search, the review found no additional clinical trials marked as “Completed” in the ClinicalTrials.gov database. Researchers terminated two clinical trials ([NCT01791465](#) and [NCT02743598](#)) due to loss of funding, and four other relevant clinical trials remained either active or were recruiting.

Summary and Gaps

The existing literature on the concomitant use of ART and GLP-1 receptor agonists in individuals with HIV showed promise but remained limited in numerous aspects. Most relevant research emerged in the last two years (2023–2024), while earlier studies offered limited insights through speculative reviews and single case studies (Dardano et al., 2022; de Lucas et al., 2015; Diamant & van Agtmael, 2012; Oriot et al., 2011; Sheffield et al., 2007). Overall, the findings broadly suggested that GLP-1 agonists had strong potential to improve weight management, glycemic control, and metabolic health in individuals with HIV, particularly those using INSTI- or TAF-based ART regimens, which contributed to weight gain (Eckard et al., 2024; Haidar et al., 2024). Despite the promising data supporting the general use of these drugs in this population, the evidence lacked robust, high-quality studies and sufficient data on long-term safety and virologic outcomes.

For instance, the majority of studies fell into lower tiers of evidence, such as expert opinions, single case studies, reviews, and small-scale observational studies, with only two completed clinical trials to date. This scarcity of high-tier evidence limited the ability to draw causal conclusions about the efficacy and safety of these combined therapies, especially in unique clinical scenarios (e.g., case of drug resistance, coinfections). Additionally, most studies suffered from small sample sizes, heterogeneous methodologies, and insufficient reporting on key outcomes. Many investigations failed to provide post-intervention data on HIV viral load and CD4 cell counts, making it difficult to assess the broader immunologic and virologic implications of GLP-1 agonist use. Given the concerns outlined regarding minor decreases in CD4 cell count (Noe et al., 2024) alongside reported increases in HIV viral load (Lake et al., 2024) with limited data, additional research and analysis were warranted to understand both

safety and efficacy when these drugs were used concomitantly. Furthermore, the variability in ART regimens, GLP-1 agonist formulations, and dosing complicated efforts to compare results across studies or generalize findings to diverse patient populations. For instance, high-tier studies exclusively evaluated semaglutide, whereas previous literature analyzed—and noted differences for—alternative GLP-1 receptor agonists, such as dulaglutide, exenatide, liraglutide, and tirzepatide (Bottanelli et al., 2023; de Lucas et al., 2015; Diamant & van Agtmael, 2012; Nguyen et al., 2024). Additionally, the two available clinical trials did not clearly outline which intraclass ARVs were used (e.g., the first-generation INSTI raltegravir or the second-generation INSTI bictegravir), potentially influencing overall clinical outcomes.

Another critical limitation involved the short follow-up periods in most studies, which prevented a comprehensive evaluation of the long-term benefits. While some studies reported adverse events, such as mild CD4 cell count reductions (Noe et al., 2024) and lipase elevations (Eckard et al., 2024), the clinical relevance and cause of these outcomes remained uncertain. The compounding effects of concomitant drug use were also understudied, given the relatively short follow-up periods. Additionally, detailed analyses of regimen-specific interactions between GLP-1 agonists and ART were notably absent, leaving clinicians with limited guidance on optimizing treatment plans for individual patients when multiple treatment options existed within each major drug class.

This systematic review and meta-analysis addressed these limitations by synthesizing the available evidence into a more cohesive framework. This approach improved statistical power, facilitated cross-study comparisons, and identified consistent patterns in efficacy and safety, where data allowed. By pooling data from multiple unique studies, a meta-analysis provided more accurate estimates of risks and benefits, offering valuable insights into ART regimens,

GLP-1 formulations, and dosing strategies. The growing interest in the use of GLP-1 agonists for individuals with HIV, due to well-known metabolic comorbidities and ART-induced weight gain, highlighted the importance of establishing a more authoritative evidence base. This study served as the first systematic review and meta-analysis to elevate the quality of evidence and support clinical decision-making for this patient population.

CHAPTER 3. METHODOLOGY

Introduction

The purpose of this systematic review and meta-analysis was to evaluate the safety and efficacy of concomitant use of ART and GLP-1 receptor agonists in people with HIV. Specifically, this study aimed to assess whether these drug classes could be used together without major adverse effects and whether their combined use maintained virologic suppression (e.g., stable HIV RNA levels and CD4 counts) while offering metabolic benefits (e.g., weight loss and glycemic control). In addition to evaluating the overall safety and efficacy of this combination, the study investigated whether intraclass differences exist (e.g., comparing dulaglutide versus semaglutide) and whether specific ART regimens (e.g., INSTI-based versus PI-based) influenced outcomes.

Research Design and Rationale

The study used a systematic review and meta-analysis design, guided by the PRISMA framework based on previous literature and PRISMA-specific resources (e.g., checklist; Agrawal et al., 2024; PRISMA, 2024). This design was appropriate for synthesizing existing literature, identifying patterns, and generating thorough conclusions regarding the safety and efficacy of concomitant ART and GLP-1 agonist use. The meta-analysis enhanced statistical power and addressed gaps in individual studies by combining data from multiple pre-existing sources. This approach aligned with the overarching goal of advancing evidence-based practices in the management of metabolic and virologic health among people with HIV, especially considering the current sparsity of literature for this demographic.

Study Variables

To achieve these goals, this study conducted a statistical review using the concomitant use of ART and GLP-1 agonists as the independent variable. The dependent variables included HIV-related outcomes (CD4 count, HIV viral load) to assess ART efficacy, metabolic outcomes (BMI, body fat percentage, weight) to assess GLP-1 efficacy, safety indicators (adverse events, including major events), and other markers (kidney function [eGFR] and liver function [liver transaminases]) to assess drug safety.

Based on the literature review, the only notable anticipated resource constraint was limited data on individual ARV drugs and specific ART regimens. However, a synthesis of available data still provided valuable insights into the concomitant use of ART and GLP-1 agonists in this population, despite these data-related constraints.

Methodology

Population

The target population included adults (≥ 18 years old) with HIV who were treated with GLP-1 receptor agonists. Most individuals included in the studies reportedly used ART concurrently. Due to the limited number of available studies for data extraction, the review included studies regardless of geographic location or clinical setting. Although the total population size remained unknown, the literature review (see Chapter 2) revealed sufficient data from case reports, cohort studies, and clinical trials to conduct meaningful analysis. By incorporating data from all eligible studies, including several relatively large cohort studies (>200 patients), the review expected the total sample size to exceed 500 cases relevant to the study population (Haidar et al., 2024; Nguyen et al., 2024).

Sampling and Sampling Procedures

This study applied a purposive sampling strategy to identify relevant studies for inclusion. To meet the inclusion criteria, eligible studies had to be peer-reviewed publications, conference abstracts, or other reputable sources that evaluated the use of GLP-1 receptor agonists in people with HIV. These studies also needed to report safety outcomes (e.g., adverse events, changes in CD4 count, or virologic failure) and/or efficacy outcomes (e.g., weight loss, glycemic control), and to be observational studies, case reports, cohort studies, or clinical trials published in English. In contrast, the exclusion criteria eliminated studies that did not involve GLP-1 receptor agonists or ART, lacked relevant outcome data or methodological transparency, or consisted of non-peer-reviewed sources, letters, or opinion pieces without empirical data.

The search strategy determined the final sample size for inclusion, and a power analysis informed subsequent meta-analytic procedures. Power calculations used a minimum effect size of 0.3 (medium effect), alpha level of 0.05, and power level of 0.80, following standard conventions for medical research (Serdar et al., 2021). GPower, a widely utilized statistical tool, supported the calculation of required sample sizes for meta-analytic comparisons. This approach contextualized the meaningfulness of identified associations and minimized the risk of type I and type II errors. GPower offered flexibility in handling different statistical tests, including those used for comparing multiple subgroups (e.g., different GLP-1 agonists and ART regimens). Sample size calculations were adjusted based on the number of eligible studies and available data to optimize statistical rigor and ensure reliable conclusions.

Data Collection Procedures

Data were extracted from archival sources, namely PubMed. Using the studies and methodology described in Chapter 2, and following the previously stated inclusion criteria, data were obtained from publicly available research studies.

Data extraction followed a standardized protocol and included study characteristics (e.g., design, sample size, location, duration), population characteristics (e.g., age, sex, HIV status), interventions (e.g., GLP-1 agonist and ART regimens), and outcomes (e.g., adverse events, HIV RNA levels, CD4 counts, weight loss, and glycemic control). The author extracted all data into a single spreadsheet and subsequently cleaned and organized it using Microsoft Excel. Given the potential for additional data beyond what was reported directly in the key studies, the author contacted corresponding authors after approval from the Institutional Review Board (IRB) to inquire about the availability of additional raw data that might offer more precise information about ART regimens, immunologic function (e.g., changes in HIV RNA or CD4 count), adverse effects (e.g., reasons for study discontinuations), or other valuable metrics for comprehensive analysis.

Instrumentation and Operationalization of Constructs

Primary safety outcomes included both rates of adverse events (e.g., changes in CD4 counts, virologic failure, gastrointestinal side effects, and metabolic complications) and severity of adverse events (e.g., “major adverse cardiovascular events” or Grade 4 events; Basch et al., 2021). Efficacy outcomes included weight loss, glycemic control (measured by changes in HbA1c), and maintenance of virologic suppression (HIV RNA <200 copies/mL).

Operational definitions included weight loss, defined as absolute or percent change in body weight, body fat percentage, or BMI. Glycemic control was measured by reduction in

HbA1c levels, expressed as absolute or percentage changes. To ensure consistency, virologic suppression was defined as HIV RNA levels below 200 copies/mL and CD4 count greater than 500 cells/mm³. Safety was assessed based on the incidence of clinically significant adverse events, including but not limited to lipase elevations, transaminase changes, cardiac abnormalities, and hypersensitivity reactions. These parameters served as indicators to collectively determine the efficacy and safety profile of GLP-1 receptor agonists when used in conjunction with ART in individuals with HIV.

Data Analysis Plan

Data analysis was conducted using two technologies to clean, organize, and analyze the available data. Microsoft Excel was used to clean and organize data, and GraphPad Prism was planned for data analysis and visualization. The analysis began with data cleaning to identify and address any missing or erroneous data. Subsequently, data organization was conducted to systematically categorize variables, including ART regimens and their respective drug classes, as available. For instance, ART drugs like Biktarvy were classified to include all active components, such as the integrase strand transfer inhibitor bictegravir and the NRTIs emtricitabine and tenofovir alafenamide.

Statistical analyses were conducted using both fixed-effects and random-effects models to calculate pooled estimates of effect sizes, including odds ratios for safety outcomes and weighted mean differences for efficacy outcomes. Subgroup analyses employed parametric tests (e.g., analysis of variance [ANOVA]) to compare different GLP-1 agonists (e.g., dulaglutide versus semaglutide) and ART regimens (e.g., INSTI-based versus PI-based). Heterogeneity among included studies was assessed using the I^2 statistic, and Cochran's Q test used to assess. Publication bias was evaluated using funnel plots and Egger's tests. All results were interpreted

using 95% confidence intervals, with adjustments applied as necessary to minimize the risk of type I errors. Publications included in the analysis were visualized using forest plots. The statistical approach and thresholds (e.g., ANOVA, confidence intervals) followed guidance from Creswell (2014), while methods specific to heterogeneity and publication bias were selected and applied in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2024).

Threats to Validity

The systematic review and meta-analysis considered several potential threats to validity. External validity was potentially impacted by heterogeneity in study designs, populations, and intervention protocols, which may have limited the generalizability of findings (Findley et al., 2021). Differences in ART and GLP-1 agonist formulations, dosing regimens, and patient demographics also introduced variability that affected comparative analyses.

Internal validity threats arose from potential biases within the included studies, such as selection bias, confounding variables, and measurement inconsistencies (Mathur & VanderWeele, 2022). The reliance on observational data increased susceptibility to residual confounding, while inconsistencies in reporting key outcomes, such as adverse events and immunologic responses (e.g., different thresholds for “HIV viral load suppression”), further limited the comprehensiveness of the conclusions. Furthermore, variation in study design, publication year, and follow-up durations introduced the possibility of historical bias and differential attrition. However, these concerns were moderated by the overall recency of research involving the target population.

Statistical conclusion validity was influenced by the quality and quantity of available data, particularly given the limited number of controlled trials. To mitigate these concerns, the

meta-analysis reviewed study heterogeneity and risk of bias within the statistical review. When possible, bias-adjusted values were used. Moreover, sensitivity analyses and subgroup evaluations were also conducted to help mitigate these limitations where possible.

Ethical Procedures

This study included the use of secondary, de-identified data, minimizing ethical risks. Permissions were obtained where required to access proprietary datasets. All data were stored securely, and confidentiality was maintained in accordance with institutional and regulatory guidelines. No direct contact with human participants occurred, eliminating the need for informed consent. However, additional data were requested from the authors of key studies in an effort to achieve a more comprehensive overall analysis.

Following approval from the IRB, an [Information Request \(Item A1\)](#) was submitted to all applicable authors to determine whether additional data were available beyond what had been reported in published studies. At the time of the request, the availability and scope of such data were uncertain. For data obtained from study authors, no personally identifiable information was collected; only aggregated or anonymized data were included in the analysis. Any datasets received from external sources underwent a secondary de-identification review before integration into the study.

All data were password-protected and stored on a secure, institutional server, with access logs monitored regularly to ensure compliance with data protection standards. Data were retained for the duration of the study and securely deleted following completion of the research and publication of findings, per institutional and ethical guidelines.

Summary

This methodology outlined the systematic review and meta-analysis process designed to evaluate the safety and efficacy of combined ART and GLP-1 receptor agonist use in individuals with HIV. Collectively, this methodology addressed key outcomes in a vulnerable population, including identifying potential intraclass drug differences and evaluating any associations between reduced efficacy and/or safety in people with HIV using GLP-1 agonists. Additionally, this methodology helped to promote new research to fill an overwhelming gap in existing literature for this population and addressed concerns related to heterogeneity, bias, and ethical guidelines. Overall, this methodology supported the study's primary aim of advancing clinical knowledge and providing evidence-based recommendations for optimizing care in this population.

CHAPTER 4. RESULTS

Introduction

The purpose of this study was to evaluate the safety, efficacy, and potential drug interactions of GLP-1 receptor agonists in people with HIV, particularly those concurrently using ART. Using a systematic review and meta-analysis guided by the PRISMA framework, this study investigated how concomitant use of ART and GLP-1 agonists affected key clinical outcomes, including weight loss, glycemic control, HIV viral load, CD4 count, and adverse events. Additional focus was placed on potential differences between specific GLP-1 formulations and ART regimens.

This study addressed three primary research questions: (1) Do GLP-1 receptor agonists produce significant metabolic outcomes (e.g., weight loss, HbA1c reduction) in people with HIV without affecting virologic response to ART? (2) Are treatment outcomes influenced by the specific ART regimen used in combination with GLP-1 therapy? (3) Is the safety profile of GLP-1 receptor agonists in people with HIV consistent with that observed in the general population?

To answer these questions, several hypotheses were tested. For metabolic efficacy, the null hypothesis stated that GLP-1 receptor agonists remained effective in people with HIV; the alternative suggested attenuated effects due to ART or HIV-related factors. For pharmacological interaction, the null hypothesis posited no significant interference from ART, while the alternative hypothesis suggested clinically relevant interactions via metabolic pathways. For regimen-specific outcomes, the null hypothesis assumed uniform (unchanged) effects across ART types, whereas the alternative proposed variable effects. Lastly, regarding safety, the null hypothesis assumed similar adverse event profiles to those with placebo and/or without HIV, while the alternative suggested differences specific to HIV or ART use.

The remainder of this chapter presents the findings from the systematic review and meta-analysis, organized to reflect both methodological rigor and clinical relevance. The Data Collection section outlines deviations from the original proposal and provides baseline descriptive data from included studies, followed by an assessment of Meta-Analysis Fidelity, ensuring transparency in data handling and analytical consistency.

The Results section investigates and reports upon the core research aims, beginning with the efficacy of GLP-1 receptor agonists in people with HIV, followed by analyses of ART effects and a focused review of GLP-1 safety profiles in people with HIV. Supplementary findings from relevant case studies are also presented to enhance context. The chapter concludes with a Summary of key findings and Transitional Commentary to set the stage for interpretation and implications in Chapter 5.

Data Collection

Data collection for this meta-analysis began with the initial literature screening phase on January 18, 2025, and continued through formal proposal development and IRB approval, which was granted on April 9, 2025. Following approval, direct inquiries were sent on April 14, 2025, to the corresponding authors of all studies that appeared to contain relevant outcome data but lacked complete numerical reporting, and/or had the potential to offer further data for subgroup analyses (e.g., on specific GLP-1 agonists or ARVs). Authors were asked to share data by April 18, 2025. Most contacts yielded no response or were unsuccessful due to invalid emails, deceased investigators, or stated limitations on data sharing. One author (Nguyen et al., 2024) provided complete raw outcome data on April 22, 2025. Data extraction, cleaning, and organization continued through July 6, 2025. This analysis primarily used the raw participant data from Nguyen et al. (2024) to represent the study's outcomes.

Deviations from Proposal Methodology

Several adjustments strengthened the original data analysis plan to ensure methodological appropriateness and practical execution, while remaining consistent with the study intent and questions. The initial plan proposed the use of GraphPad Prism for statistical computations and visualizations. However, GraphPad proved insufficient for meta-analytic procedures, particularly those involving multiple study designs and effect size modeling. As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, RevMan was briefly used to calculate standard deviations from available data (e.g., using mean, 95% confidence interval, and sample size). Although initially designed as the primary meta-analysis tool, RevMan was found to be incompatible with analyses involving mixed study designs, as outlined in Chapter 10.4.4.1 (Higgins et al., 2024). Consequently, Jamovi was selected as the primary platform for data analysis due to its scientific validity, open-access availability, and robust meta-analytic capabilities, including effect size calculations, heterogeneity assessment, and integrated visual outputs such as forest plots (Calin-Jageman & Cumming, 2024; Cumming & Calin-Jageman, 2024). These features aligned with statistical guidance from Creswell (2014) and Higgins et al. (2024).

Further review of the *Cochrane Handbook for Systematic Reviews of Interventions* and availability of cleaned data supported the use of inverse variance meta-analyses to evaluate primary outcomes and mean effect (M) of pooled outcomes. The use of a meta-analysis of means was chosen due to the heterogeneity in the data, which reduced the applicability of traditional ANOVA or MANOVA tests that do not adjust for sample size or variance. Because Jamovi's built-in modules did not support Egger's test or funnel plots using mean/SD inputs, which were

the predominant format of available data, a study-based bias assessment (risk of bias; RoB) was also conducted, in accordance with Cochrane guidance (Higgins et al., 2024).

Power analysis was performed using GPower to confirm the adequacy of the pooled sample size in detecting medium effects across selected outcomes. To account for bias, power analysis used bias-adjusted values for Cohen's d , often referred to as Hedges' g , enhancing internal validity. The final statistical approach primarily included random-effects meta-analysis (fixed-effects used for additional comparison rarely). Tests for heterogeneity included I^2 , τ^2 (tau-squared), T (tau), and H^2 . The Q-statistics were unavailable to evaluate heterogeneity with the analytic package used, but the four measurements provided sufficient insight.

Regression-based correlation analyses were also performed to explore associations between variables, such as weight change, BMI, HbA1c, GLP-1 type, ARV class, baseline characteristics, and follow-up duration. These correlation analyses included scatterplots with lines of best fit and reported Pearson's r values. These exploratory procedures were incorporated due to the nature of the available data and were deemed scientifically appropriate for characterizing potential relationships between clinical outcomes, especially in the context of limited data and gaps in the research.

Lastly, several subgroup analyses utilized general linear modeling (GLM) to investigate specific subgroup effects and patterns, using raw data from one included study (Nguyen et al., 2024). These models evaluated the effect of ARV class and semaglutide dose on weight loss outcomes, with up to 10,000 bootstrap samples applied to improve the robustness of confidence interval estimates and reduce reliance on parametric assumptions. Standard tests such as ANOVA and t-tests, which assume homogeneity in study design or data, were less suitable given the limitations of the data available for this meta-analysis. To enhance model precision, follow-

up duration was included as a covariate in a multivariate GLM, providing a more detailed understanding of time-adjusted effects across dosage strata that traditional parametric tests may not have captured. Assumptions of homogeneity of variance and homoscedasticity were evaluated using Levene's test and the Breusch–Pagan test, respectively, adding validity to the use of linear modeling techniques and informing the interpretation of subgroup findings. The GLM model applied an ANOVA omnibus test adjusted for heteroscedasticity, making it more appropriate for this study, given concerns regarding variance. In one of the bootstrapped GLM analyses, a post hoc Bonferroni correction was applied to minimize the risk of type I error.

These methodological adjustments were made to maintain the scientific rigor of the study while accommodating practical constraints encountered during data collection and analysis, and were primarily guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2024).

Baseline Descriptive Data

This study conducted a primary meta-analysis on five studies. Subsequently, five additional case studies were reviewed and analyzed to corroborate small-scale trends that appeared within the primary analysis. Two more studies were referenced contextually, but no formal analysis was conducted using them due to a lack of applicable outcome data. This approach aligned with PRISMA guidelines, and [Figure A1](#) represents the selection of studies. [Table A3](#) presents the baseline descriptive characteristics of the studies analyzed.

This meta-analysis sample was derived from five studies with various methodological designs, including retrospective cohorts, one single-arm clinical trial, and one RCT, reflecting the limited but emerging literature on GLP-1 receptor agonist use among people with HIV. Given the use of purposive sampling and the lack of population-level registries on this

population, a non-probability sampling approach was necessary. As such, generalizability is inherently limited; however, the sample appears reasonably representative of the population of interest within the constraints of current literature.

All included studies recruited adult populations with HIV, documenting GLP-1 agonist use alongside active ART in most study participants. Age distributions matched the demographic profile of people aging with HIV, with mean ages ranging from 50 to 58 years, consistent with epidemiologic data indicating that a growing proportion of people with HIV in high-income settings are over age 50 (Lyons et al., 2022). The pooled sample ($N = 567$) consisted predominantly of males (approximately 76%), reflecting broader trends in HIV epidemiology, particularly within US-based cohorts, though it likely underrepresented cisgender women and transgender persons. One study was the only one to report transgender participant representation, which further limited external validity for gender-diverse populations at higher risk of HIV infection. Due to inconsistent reporting, geographic and racial/ethnic diversity could not be fully assessed. However, the included studies collectively provided a clinically relevant cross-section of the target population, especially in terms of age, sex distribution, and ART-treated status, including modern ART regimens and GLP-1 agonists, given the recency of all published data (within the past three years). As such, although the non-randomized sampling approach and underrepresentation of certain subgroups posed limitations, the sample proportionally aligned with the demographic features of the population most likely to be affected by the clinical question under investigation.

The meta-analysis primarily used aggregated study-level data rather than individual-level participant data. Therefore, it did not test covariates using standard univariate procedures. While it descriptively reviewed demographic characteristics, such as age and sex, the limited number of

studies and variability in reported data precluded formal covariate modeling. Instead, the analysis considered relevant variables, such as study design, sample size, and GLP-1 formulation, narratively or through subgroup comparison where feasible.

Meta-Analysis Fidelity

While the data collection and analytical processes largely followed the procedures outlined in Chapter 3, several challenges required adjustments to the original plan from an analytical standpoint. The most significant deviation was related to limited data availability. Despite contacting all corresponding authors of eligible studies, most did not respond or were unable to share raw data. Only one study (Nguyen et al., 2024) provided complete individual-level data, which arrived fully de-identified. As a result, all other analyses relied on aggregate, study-level data, which required extensive cleaning and estimation to standardize outcomes for synthesis.

In multiple cases, studies did not directly report standard deviations, so these were estimated using either RevMan or conventional statistical formulas based on available medians, interquartile ranges, and confidence intervals. Additionally, one study omitted BMI change (Haidar et al., 2024), which was reverse calculated using the relationship between weight, height, and BMI. Although RevMan initially supported these efforts, it ultimately proved inadequate for the primary meta-analysis due to its limitations with single-arm trials, and only one study had multiple arms. GraphPad Prism was also excluded from final analyses due to limited meta-analytic functionality. Instead, Jamovi served as the primary analysis platform based on its open-source accessibility, integrated effect size modeling while accounting for heterogeneous samples, and capacity for visual output such as forest plots, funnel plots, and correlation scatterplots.

Jamovi was selected for use after identifying its utility for meta-analyses and by subsequently testing the functionality of this software with the prepared aggregate data.

These adaptations ensured data quality and methodological rigor despite limitations in the primary source data. A complete description of estimation formulas and procedures appears in [Appendix A \(Item A2\)](#).

Results

As noted above, the primary meta-analysis involved five studies. [Table A3](#) presents the overall descriptive statistics for the included studies. A brief secondary analysis was also conducted on five additional case studies, each with a sample size of one. The descriptive characteristics and associated outcomes for these case studies are presented in the [Case Studies](#) section.

The study evaluated the primary five studies for methodological quality and potential for internal bias using the Cochrane RoB Tool. This framework evaluated domains, such as selection bias, performance bias, detection bias, and attrition bias. Most retrospective studies were rated as having either an unclear or high risk of bias due to limitations in blinding, lack of randomization, and incomplete outcome reporting. The single randomized controlled trial (Eckard et al., 2024) demonstrated low risk of bias across most domains. Detailed domain-level assessments for each study appear in [Appendix A \(Item A3\)](#). Although several studies were rated as “High risk of bias” overall per RoB criteria, this rating reflected a conservative application wherein any single domain rated as high risk resulted in a high overall rating. Notably, some studies (e.g., Lake, 2024; Nguyen, 2024) demonstrated strong methodological rigor but were rated high overall due to limitations inherent to single-arm or retrospective designs.

The meta-analysis evaluated statistical assumptions based on the nature of the pooled data and the methods applied. Because the analysis relied on aggregated, study-level data, individual-level assumptions, such as normality of residuals or homogeneity of variance, were not applicable. Instead, the study examined assumptions related to meta-analytic validity—namely, independence of effect sizes, consistency of outcome measurement, and heterogeneity across studies. Effect sizes were independently derived from each included study, with no duplicated populations or overlapping samples. Heterogeneity was assessed using the I^2 index and coupled with supplementary outcomes, such as H^2 , T , T^2 , and the diamond ratio, each of which guided the decision to apply random-effects models in analyses with moderate to high between-study variability. Overall, the statistical assumptions required for valid meta-analytic synthesis were adequately met, and appropriate adjustments were made when variability or potential bias was observed. Of note, statistical significance was reported with $p < .05$.

Efficacy of GLP-1s in People With HIV

Question 1: Do GLP-1 receptor agonists produce significant metabolic outcomes (e.g., weight loss, HbA1c reduction) in people with HIV without affecting virologic response to ART?

Absolute and Monthly Metabolic Outcomes

A meta-analysis assessed four primary metabolic outcomes: absolute weight change (kg), percent body weight change, BMI change, and HbA1c change. A random-effects model accounted for heterogeneity across study designs and populations. The pooled estimates for each outcome demonstrated a statistically significant reduction ($p < .001$), supporting the alternative hypothesis that GLP-1 receptor agonists yield meaningful metabolic effects in people with HIV. For example, BMI decreased by a pooled estimate of -1.93 (95% CI $[-2.72, -1.15]$; SE = 0.400; $k = 5$), as shown in [Figure A2](#), with similarly significant reductions observed across other

metabolic indicators. While one study did not show significant effects in isolation across some outcomes (e.g., Bottanelli et al. [2023], weight change), the combined analysis demonstrated robust treatment effects across all included outcomes.

Heterogeneity for the four primary outcomes was assessed across studies using metrics generated from the random-effects model, including I^2 , τ^2 , T , and H^2 . I^2 values across the four primary outcomes ranged from 84.3% to 94.3%, indicating high to considerable heterogeneity, depending on the outcome. For example, the BMI change analysis yielded an I^2 of 92.6%, τ^2 of 0.74, and H^2 of 13.61, suggesting substantial between-study variance. These values supported the use of a random-effects model to account for expected clinical and methodological variability across included studies.

The obvious heterogeneity among the studies included in this meta-analysis could be partly attributed to varying follow-up durations. As such, the mean change for each of the key metabolic outcomes was formulated into monthly changes to further evaluate the time-dependent effects of GLP-1 agonists. In addition to the analysis of HbA1c change, the Bottanelli et al. (2023) study was excluded from the analysis of monthly percent weight change. The absolute percent weight change (both mean and standard deviation) was calculated using estimated values, and further calculation and estimation were deemed counterintuitive to the validity of this analysis. Overall, GLP-1 agonists demonstrated a significant ($p < .001$) effect on all four parameters when adjusted to monthly values. [Figure A3](#) provides a forest plot demonstrating monthly weight changes between studies.

Moreover, every measured outcome demonstrated statistical significance for each study when adjusted to monthly changes, except for those from the Bottanelli et al. (2023) study (weight change, BMI). I^2 values across the four primary outcomes had more variance, with three

parameters (weight change in kg, percent weight change, and BMI) demonstrating values of 96.5% or higher (considerable heterogeneity), while HbA1c was just 45.2% (moderate heterogeneity).

The study conducted a post hoc power analysis on absolute values to evaluate whether the effect size of the reported data was sufficient, specifically for mean weight change (kg). The analysis utilized bias-adjusted effect sizes for both fixed-effects and random-effects models. Both models demonstrated statistically significant meta-analytic effects, with cumulative meta-analytic effect sizes of -0.720 (95% CI $[-0.813, -0.626]$) and -0.827 (95% CI $[-1.10, -0.551]$) for the fixed-effects and random-effects models, respectively. [Figure A4](#) (random effects) and [Figure A5](#) (fixed effects) display these results via forest plots. Moreover, both models demonstrated high power (1.00), with similar output parameters recorded for the fixed-effects (noncentrality parameter -17.1 , critical $t -1.96$) and random-effects models (noncentrality parameter -19.7 , critical $t -1.96$). Given the magnitude of this power score, no additional post hoc power analyses were performed on the remaining metabolic outcomes.

Variations in GLP-1 Usage

The subanalysis compared the effects of semaglutide-only studies versus those that used more than one GLP-1 agonist, given the variability in GLP-1 treatment options and the overall study designs. For instance, both Nguyen et al. (2024) and Bottanelli et al. (2023) used semaglutide, dulaglutide, and liraglutide, while Nguyen et al. (2024) also included exenatide and tirzepatide. The subanalysis used GLP-1 usage as a moderator (semaglutide versus varied GLP-1). While three studies contributed to the semaglutide group and two to the varied GLP-1 group, each group included a larger cohort study (e.g., Haidar for semaglutide, $n = 222$; Nguyen for varied, $n = 227$), which balanced the total sample despite heterogeneity in study designs.

Importantly, Bottanelli et al. (2023) did not provide usable data for HbA1c, so meta-analytic statistical analyses required at least two studies with available data in both groups to proceed.

For the three measured outcomes (weight change in kg, percent weight change, BMI change, and HbA1c change), the semaglutide subgroup produced statistically significant reductions ($p < .001$) under a random-effects model. The varied GLP-1 group only demonstrated statistically significant effects (using a threshold of $p < .05$) for BMI change ($p = .040$). Weight change in kg ($p = 0.060$) and percent weight change ($p = 0.057$) were near but above statistical significance. Moreover, moderator analysis suggested a statistically significant difference between groups in terms of weight change (kg) ($M = 4.39$, 95% CI [0.352, 8.43], $p = 0.033$), weight change (%) ($M = 4.28$, 95% CI [0.352, 8.21], $p = 0.033$), and BMI ($M = 1.47$, 95% CI [0.155, 2.78], $p = 0.028$). [Figure A6](#) demonstrates the moderator analysis for BMI.

The lower effect strength in the varied GLP-1 group resulted from the inclusion of the Bottanelli (2023) study, which did not report statistically significant reductions in weight (kg or percent) or BMI, and to the absence of a third sample, unlike the semaglutide group.

Heterogeneity estimates supported this conclusion. For weight change (kg), percent weight change, and BMI change, the I^2 values in the varied GLP-1 group were 96.52%, 95.68%, and 95.4%, respectively, indicating considerable heterogeneity. In contrast, the semaglutide group showed much lower heterogeneity: 20.95%, 76.93%, and 53.28% for the same outcomes, corresponding to low to substantial heterogeneity. The τ^2 and H^2 values further confirmed the disproportionate influence of the Bottanelli (2023) study on weight-related effect sizes. In the varied GLP-1 group, τ^2 and H^2 were up to 69.8 and 22.7 times higher, respectively, than in the semaglutide group. These results suggest that the Bottanelli study introduced disproportionate

variability due to its relatively small sample size, lack of consistent outcome significance, and inclusion of multiple GLP-1 agents.

Together, these subgroup findings suggest that semaglutide may offer more consistent metabolic benefits in people with HIV compared to varied GLP-1 agents, though small sample sizes and heterogeneity in study designs may have skewed the magnitude of outcomes in the varied GLP-1 group.

To further examine GLP-1-specific effects on metabolic outcomes, a tertiary subgroup analysis was performed. Prior to this, the raw data provided by Nguyen et al. (2024) were analyzed, organized, and cleaned to align outcomes and units with those of other studies. The inclusion of these data allowed for a descriptive comparison of individual GLP-1 receptor agonists in people with HIV, specifically semaglutide, dulaglutide, liraglutide, exenatide, and tirzepatide. [Figure A7](#) shows the observed changes. While aggregate effects across all GLP-1 agents remained statistically significant ($p < .001$), formal subgroup comparisons could not be performed due to limited study representation; only semaglutide was included in more than one study. Nonetheless, descriptive trends were notable. Semaglutide elicited statistically significant reductions in all four metabolic outcomes across all four contributing studies ($p < .001$).

Dulaglutide and tirzepatide also showed favorable profiles, with dulaglutide achieving statistical significance for all outcomes ($p \leq .001$), and tirzepatide achieving significance for all outcomes except HbA1c ($p = .154$). In contrast, liraglutide and exenatide did not demonstrate statistically significant changes in any measured outcome. However, the small sample sizes ($n = 7$ and $n = 2$) and outliers in the raw data likely attenuated observable effects for these agents. These exploratory findings offer preliminary insight into drug-specific trends that warrant further investigation in larger and more diverse clinical samples.

Dosing Differences

While the overall effects of GLP-1 usage appeared to be positive toward metabolic outcomes, it is important to recognize the different doses used to elicit clinical outcomes and the variance in outcomes that different doses may cause. Although data remain limited in this regard, [Table A4](#) describes the general differences in dosing, follow-up, and weight loss (kg) outcomes among included studies. Importantly, some studies included different GLP-1 agonists (e.g., Nguyen et al., 2024) and/or different dosing approaches, including both quantity and administration type (i.e., subcutaneous versus oral; Haidar et al., 2024).

Given the variability in dosing methodology among these studies, it was deemed most appropriate to summarize the study parameters and compare the effects of controlled studies (e.g., Eckard et al., 2024; Lake et al., 2024) versus similar outcomes in people without HIV. These data are reported in the [Effects Versus People Without HIV](#) section below.

This study conducted a general linear model to evaluate whether GLP-1 dose influenced weight loss in people with HIV, using raw data from Nguyen et al. (2024) for semaglutide (the agent with the largest sample). Doses were grouped into three categories: ≤ 1.0 mg (subcutaneous, $n = 41$), 1.7–2.4 mg (subcutaneous, $n = 73$), and 7–14 mg (oral, $n = 19$). Follow-up duration (in months) served as a covariate to account for time-dependent changes in weight loss. Bootstrapping with 10,000 samples was applied to strengthen reliability given modest sample sizes and assumption violations. The overall model was statistically significant ($R^2 = 0.064$, $F = 2.94$, $p = 0.036$), indicating that semaglutide dose and follow-up duration together explained a small but meaningful portion of variance in weight change. Dose group remained a significant predictor after adjusting for follow-up time ($F = 3.22$, $p = 0.043$), with a small to moderate effect size (partial $\eta^2 = 0.039$). Follow-up duration itself approached significance ($F =$

3.46, $p = 0.065$), with an estimated average of 0.438 pounds lost per additional month of follow-up (95% CI [-1.007, 0.054]). [Figure A8](#) presents the differences in semaglutide dose and follow-up duration on weight loss.

Post hoc comparisons using Bonferroni correction revealed no significant differences between the ≤ 1.0 mg group and either the 1.7–2.4 mg group ($p = 0.388$) or the 7–14 mg group ($p = 0.364$). However, a significant difference emerged between the 1.7–2.4 mg group and the 7–14 mg group ($p = 0.038$), with the higher-dose oral group losing substantially less weight on average (mean difference = -11.01 lbs; Cohen's $d = -0.558$). These results suggest that the 1.7–2.4 mg subcutaneous dose may produce greater weight loss than higher-dose oral semaglutide, even at shorter follow-up intervals. Tests of model assumptions revealed potential violations of homoscedasticity (Breusch–Pagan, $p = 0.019$) and homogeneity of variances (Levene's test, $p = 0.003$). These findings reinforce the need for cautious interpretation and support the use of bootstrapping to increase analytic robustness.

Together, these findings suggest that semaglutide dose and treatment duration both contribute to weight loss among people with HIV. Notably, individuals receiving 1.7–2.4 mg subcutaneous semaglutide experienced the most pronounced weight loss, even when accounting for shorter follow-up periods.

Observed Correlations

To further evaluate the positive effects of GLP-1 agonists, especially in the context of limited clinical data, additional correlation analyses were developed to identify noteworthy correlations. Pearson's r was calculated, and the data presented are based on the following thresholds:

- $|r| = 1$: Perfect positive (1) or negative (-1) correlation
- $0.7 \leq |r| < 1$: Strong correlation
- $0.5 \leq |r| < 0.7$: Moderate correlation
- $0.3 \leq |r| < 0.5$: Weak correlation
- $|r| < 0.3$: Negligible or no correlation

Numerous correlation analyses were conducted based on the Principle of Diminishing Returns, in which outcomes with greater potential for change will exhibit the most change, but that change becomes blunted as the potential for change lessens. As such, mean baseline weight was evaluated against all four primary outcomes, demonstrating a strong correlation with changes in HbA1c ($r = -0.84$), BMI ($r = -0.71$), and weight in kg ($r = -0.73$; see [Figure A9](#)), as well as a moderate correlation with change in percent weight ($r = -0.66$). When evaluating versus monthly values, only HbA1c change exhibited a strong correlation ($r = -0.79$) with mean baseline weight. This data suggests that mean baseline weight may be a more viable predictor of overall weight loss than the amount of weight lost on a per-month basis.

Interestingly, baseline BMI demonstrated somewhat comparable results to the previous correlations with baseline weight, but not identical. For instance, weight-related parameters demonstrated a moderate to high ($r = -0.68$ to -0.73) correlation with baseline BMI but only a weak correlation with change in HbA1c ($r = -0.45$). When adjusted for monthly values, baseline BMI did not exhibit a strong correlation with any of the four metabolic outcomes, including a negligible correlation with monthly percent weight change ($r = 0.04$).

To further evaluate the potential for time-dependent associations between GLP-1 agonist usage and metabolic outcomes, correlations between follow-up duration and both absolute and monthly outcomes were examined. In alignment with baseline weight, follow-up duration established a high negative correlation ($r = -0.7$) with change in HbA1c. The three weight-based parameters showed moderate, positive correlations with follow-up ($r = 0.60$ to 0.68). These data suggest that people with HIV would lose less weight with increasing duration of GLP-1 agonist use. When adjusted to monthly values, each of these correlations trended less favorably. Follow-up duration established a weak negative correlation with monthly HbA1c change ($r = -0.32$), and strong, positive correlations with monthly changes in weight loss (kg) ($r = 0.91$), percent weight loss ($r = 0.99$), and BMI ($r = 0.91$). These data further reinforce the idea that increasing the duration of GLP-1 usage leads to less substantial weight loss on a monthly basis.

Immunologic Function and Virologic Control

Inconsistent and incomplete reporting of HIV-related outcomes limited the assessment of immunologic and virologic control across studies. While all assessments included studies reported baseline CD4 counts, most did not provide longitudinal data on CD4 or viral load (VL); where such data were included, formats varied considerably. As a result, a formal meta-analytic synthesis of immunologic outcomes was not possible. [Table A5](#) outlines the availability and format of such data in the five primary studies.

Baseline CD4 values were relatively consistent across studies, with means ranging from 743.8 to 818 cells/mm³ in the five studies that reported them. These values suggest that most participants had well-preserved immune function at study entry. However, changes in CD4 over time were only reported in one study (Lake et al., 2024), which showed a modest decrease from a mean of 762 to 730 cells/mm³ over 24 weeks (absolute change: -14.0 ; 95% CI $[-81.1, 53.1]$).

While the lower bound of the confidence interval indicates a potentially meaningful decrease in some cases, the high variability and overlapping confidence intervals limit firm conclusions. The possibility of transient CD4 suppression has been raised in previous literature that demonstrated a median decrease of approximately 60 cells/mm³ among 70 people with HIV who initiated either semaglutide or dulaglutide (Noe et al., 2022). Collectively, these outcomes may merit further investigation in subpopulations with compromised immune function or untreated HIV.

VL data were similarly limited. Overall, five studies reported baseline VL using categorical thresholds rather than continuous measures, but with two different thresholds (<50 copies/mL and <400 copies/mL) observed. Moreover, the scope of VL measurement was limited in some studies. For example, Bottanelli et al. (2023) reported that all participants had VL <50 copies/mL, but did not assess change over time. Lake et al. (2024) noted that 100% of participants had VL <50 copies/mL at baseline, and 97.9% maintained suppression at 24 weeks, though no explanation was provided for the three individuals who exceeded this threshold. Eckard et al. (2024) reported VL <400 copies/mL for 53 of 54 participants at baseline, with maintenance of suppression over the study period. Notably, Eckard et al. (2024) used a higher threshold (<400 copies/mL), deviating from the standard threshold of virologic suppression (<200 copies/mL) and/or undetectable VL (<50 copies/mL). Haidar et al. (2024) and Nguyen et al. (2024) each reported baseline suppression rates (~89%), but did not assess longitudinal VL trends.

Exploratory analysis of raw data from Nguyen et al. (2024) suggested that baseline virologic suppression may not significantly affect the metabolic efficacy of GLP-1 receptor agonists. Among individuals with VL >50 copies/mL ($n = 25$), the mean weight loss was -5.23 kg (SD = 8.44) compared to -5.30 kg (SD = 8.52) among those with VL <50 copies/mL ($n =$

202). Similarly, no strong associations were observed between CD4 count and weight loss, with individuals as low as 12 cells/mm³ still demonstrating clinically meaningful reductions in body weight. These exploratory findings suggest that GLP-1 receptor agonists may remain effective for weight loss in people with advanced HIV, including those with uncontrolled viremia or low CD4 counts.

Together, these findings indicate that no major immunologic or virologic harm has been observed; however, the absence of standardized, longitudinal data across studies limits definitive conclusions. Further investigation is warranted to assess the long-term immunologic safety of GLP-1 receptor agonists in people with HIV, particularly among those with advanced disease or poor ART adherence.

Effects Versus People Without HIV

Alongside evaluating the overall effectiveness of GLP-1 agonists in people with HIV, this systematic review and meta-analysis aimed to determine if the outcomes were comparable to people without HIV. The capacity to equivocally evaluate the effectiveness was blunted by a lack of data for people with and without HIV using comparable methodology. For instance, both Eckard et al. (2024) and Lake et al. (2024) used semaglutide 1.0 mg in non-diabetics for 24 to 32 weeks. No such studies were identified with the same study characteristics (i.e., dosage, diabetes status, and study duration). [Table A6](#) outlines mean weight loss outcomes from studies that used an identical dose and comparable treatment durations, with mean weight loss ranging from 4.5 kg to 7.87 kg over 24 to 40 weeks. Moreover, [Figure A10](#) visualizes the differences in weight change (kg) from each of these studies.

As noted, the SUSTAIN studies were not conducted among people with HIV. Moreover, these studies were conducted on people with T2DM (Ahrén et al., 2018; Frías et al., 2021). Thus,

despite the otherwise similar study dynamics, the studied populations do have notable pathological differences that could influence the associated outcomes. Importantly, evidence suggests that non-diabetics experience greater weight loss with semaglutide use than diabetics. However, evidence comparing the effectiveness of an equivalent dose of semaglutide (1.0 mg once weekly) and for a similar duration is largely unavailable among non-diabetics.

Researchers have documented a dose-dependent relationship between semaglutide and weight loss. These findings suggest a dose exceeding 1.0 mg once weekly may elicit greater weight loss in people with or without HIV. One retrospective study reported a mean reduction in weight of -10.5 kg (SD, 6.8 kg; 95% CI [-11.2, -9.3]) with semaglutide 2.4 mg for 24 weeks among 343 obese or overweight people with and without diabetes. Thus, it could be expected that people with HIV could experience greater weight loss with a greater dose, if tolerated.

A second study compared patients with and without diabetes who used different semaglutide doses over six months, demonstrating that higher doses ($n = 60$; 1.7 mg or 2.4 mg) produced 2.9% greater weight reduction than lower doses ($n = 42$; 0.25 mg, 0.5 mg, and 1.0 mg) in six months ($p = .01$) (Ghusn et al., 2022). A meta-analysis evaluating the effectiveness of GLP-1 agonists (not exclusively semaglutide) in non-diabetics calculated a mean decrease in body weight of -3.20 kg (34 studies; $n = 9,480$; 95% CI [-3.81, -2.59]) for studies with a follow-up period less than a year and including both diabetics and non-diabetics (Wong et al., 2025). After accounting for all variables (e.g., dosage used, study duration, diabetes status), the available data suggest that people with HIV experience comparable weight loss to the general population, despite the lack of explicit data for comparison.

Effect of Antiretroviral Drugs on GLP-1 Agonists

Question 2: Are treatment outcomes influenced by the specific ART regimen used in combination with GLP-1 therapy?

Evidence suggests that certain ARV drugs contribute to disproportionate weight gain in people with HIV, specifically tenofovir alafenamide (TAF) and ARVs in the INSTI class (Capeau et al., 2024; Surial et al., 2021). As such, one of the foci of this meta-analysis was to identify whether certain ARV drugs affected the efficacy of GLP-1 agonists. The lack of ARV-specific data made any potential analysis of TAF use unfeasible; however, enough INSTI-specific data were available to include within this meta-analysis and systematic review. Notably, only two studies (Haidar et al., 2024; Nguyen et al., 2024) provided outcomes directly related to INSTI use. These studies compared weight loss between participants who did and did not use an INSTI in their ART regimen.

Given that many modern ART regimens include INSTIs, a much greater proportion of the total sample was represented in the INSTI group. For example, Haidar et al. (2024) and Nguyen et al. (2024) reported INSTI use in 183 and 169 subjects, respectively; collectively, a total of 61 subjects were explicitly represented in the non-INSTI group. Note, for the analysis of the Nguyen et al. (2024) data, the analyses excluded studies marked as “Multidrug regimen not listed above.” Independently, both studies demonstrated statistically significant reductions in weight (kg) in both the INSTI group ($p < .001$ for both studies) and the non-INSTI group (Haidar, $p < .001$; Nguyen, $p = .003$), as shown in [Figure A11](#). Collectively, both the INSTI group (-5.78 , 95% CI $[-6.80, -4.76]$) and non-INSTI group (-6.33 , 95% CI $[-7.95, -4.70]$) demonstrated statistically significant reductions in weight (kg) ($p < .001$), though overall weight loss was slightly greater in the non-INSTI group. Moderator analysis demonstrated no significant

between-group effect for weight loss with or without INSTI use ($p = 0.311$). Interestingly, the range of outcomes in the non-INSTI group appeared larger in those from the Nguyen et al. (2024) study ($M = -6.10$, 95% CI $[-9.97, -2.23]$) compared to the Haidar et al. (2024) study ($M = -6.38$, 95% CI $[-8.10, -4.66]$). These differences could be attributable to the varied GLP-1 agonists used in the Nguyen et al. (2024) study.

In addition to the above analysis, correlations were calculated between the proportion of study subjects using an INSTI and all four primary clinical outcomes. All studies reported the proportion of study subjects using an INSTI, ranging from 33.33% to 83.0%. Strong correlations were observed between INSTI usage (% of subjects) and weight loss in kg ($r = -0.97$; see [Figure A12](#)), percent weight loss ($r = -0.93$), and BMI ($r = -0.96$). In contrast, a negligible correlation was observed for change in HbA1c ($r = 0.033$). Altogether, these data suggest that GLP-1 agonists remain effective (and possibly superior) in the context of INSTI use, and metabolic outcomes are comparable to those observed in people not taking this class of ARV with concerns of associated weight gain. However, the Bottanelli et al. (2023) study may have served as a critical outlier in the correlation analysis. For instance, that study reported the lowest utilization of INSTIs (33.3%) compared to all other studies (at least 74.9%) and exhibited the fewest weight-related changes, which likely skewed the data to resemble a linear line. Importantly, the Bottanelli et al. (2023) study was *not* included in the only correlation analysis that yielded a negligible result. Further studies should confirm that all intended outcomes (e.g., reduction in HbA1c) are positively affected, regardless of which ARV classes are used in a treatment regimen.

To further validate the small interclass differences between INSTIs and other ARV classes, a generalized linear model was conducted using raw patient-level data from Nguyen et

al. (2024) to assess differences in weight loss between individuals prescribed INSTI-based versus non-INSTI ARV regimens. Bootstrapping (10,000 iterations) was applied to improve estimated reliability. Results demonstrated no significant difference between groups ($p = 0.653$; see [Figure A13](#)), with an estimated mean difference of 1.999 lbs (0.90 kgs) and a minimal R^2 of 0.001. Effect size indices (η^2 , ω^2 , ε^2) were ≤ 0.001 , further indicating negligible impact. Tests showed that the data met the necessary assumptions for this analysis, including similar variability between groups (Levene's test, $p = 0.126$) and consistent spread of data (Breusch–Pagan test, $p = 0.400$). These results suggest that ARV class was not a meaningful predictor of weight loss within this cohort of GLP-1 agonist users with HIV.

GLP-1 Safety in People With HIV

Question 3: Is the safety profile of GLP-1 receptor agonists in people with HIV consistent with that observed in the general population?

This meta-analysis aimed to evaluate two key relationships for GLP-1 agonists in people with HIV: efficacy and safety. However, limited data were available regarding adverse effects or other safety parameters for GLP-1 agonists in people with HIV. Only two of the five studies reported on adverse effects. Nguyen et al. (2024) reported broadly that, of all participants, only 10 (4.4%) discontinued GLP-1 usage or changed to an alternative GLP-1 agonist due to intolerance. The Eckard et al. (2024) study provided a more comprehensive overview of adverse effects, but categorized them only as either study-related or non-study-related, without clearly explaining how the determination was made. As such, this meta-analysis and systematic review aimed to identify and discuss adverse effects with notable differences between groups (semaglutide versus placebo) regardless of study-related or non-study-related classification.

In this review, adverse events were manually assessed and classified based on their relative frequency in the semaglutide versus placebo groups. Risk levels were categorized as low, moderate, or high, based on observed differences in incidence, clinical relevance, risk difference, and confidence interval margins. Low-risk adverse effects had a relative risk difference of less than 5%, moderate risk between 5% and 10%, and high-risk events >10%.

Overall, study-related adverse events demonstrated a generally favorable safety profile for semaglutide. Most events were classified as low risk, including elevations in lipase (7% vs. 4%), creatinine (2% in both groups), and gastrointestinal symptoms, such as nausea, vomiting, and dyspepsia. Notably, appetite changes occurred more frequently in the semaglutide group (13% vs. 2%) and were classified as high risk due to both magnitude and potential implications for patient adherence or nutritional balance, with a relative risk difference of over 11%. Interestingly, diarrhea or loose stools were observed in 13% of placebo recipients but not reported in the semaglutide group, suggesting a potential protective effect in this sample.

Among the non-study-related events, several findings were classified as high risk based on absolute differences exceeding 10% and potential clinical impact. Elevated creatinine occurred in 44% of semaglutide recipients compared to 24% in the placebo group (risk difference: 20.4%; 95% CI [2.4%, 36.9%]). Although semaglutide is not typically associated with direct nephrotoxicity, this finding may reflect either background renal impairment in the population or a sign of clinical relevance that warrants further investigation.

Dyspepsia was reported in 20% of semaglutide recipients but in none of the placebo group, yielding a significant relative difference (risk difference: 20.4%; 95% CI [8.4%, 30.9%]). Constipation or irregular bowel movements (30% vs. 9%) and appetite changes (15% vs. 7%) also met high-risk criteria, both of which are consistent with known gastrointestinal side effects

of GLP-1 receptor agonists. In contrast, elevated glucose was significantly more common in the placebo group (72% vs. 46%), with a negative risk difference of 25.9% (95% CI [-42.6%, -7.4%]), suggesting a potentially protective glycemic effect of semaglutide even within this short trial duration. Events classified as moderate risk included nausea, vomiting, general gastrointestinal complaints, and diarrhea or loose stools. These were commonly observed in both groups, but slightly more prevalent in the semaglutide arm based on non-study-related data.

[Table A7](#) shows the adverse effects and their corresponding classifications.

While many findings align with known effects of GLP-1 receptor agonists (e.g., appetite suppression, GI discomfort), the notably high incidence of elevated creatinine and dyspepsia among semaglutide users, especially in events not attributed to the study, raises concerns. These patterns suggest the need for careful patient selection, especially for individuals with pre-existing renal or gastrointestinal conditions. However, it is unclear whether these events reflect true drug-related risk or are confounded by underlying disease or other variables, given the secondary nature of this analysis and the small sample size ($N = 54$ per group).

Discontinuations due to adverse effects occurred in 7% of semaglutide participants compared to 2% in the placebo group, earning a moderate-risk designation. However, no life-threatening events or severe toxicities traditionally associated with GLP-1 receptor agonists (e.g., pancreatitis, anaphylaxis) were reported. Most adverse events were mild to moderate in severity. These findings support the need for ongoing surveillance and tailored counseling for patients prescribed GLP-1 receptor agonists, particularly among people with HIV, as comorbidities may increase their susceptibility.

Importantly, the Eckard et al. (2024) study also noted the potential for protective effects that may outweigh the aforementioned adverse effects, most of which were low in severity. For

instance, semaglutide use among people with HIV demonstrated statistically significant improvements ($p < .01$) in weight, BMI, waist circumference, total body fat, total limb fat, trunk fat, abdominal total adipose tissue, abdominal visceral adipose tissue, and HbA1c, and notable improvements ($p < .05$) in glucose, homeostatic model assessment of insulin resistance (HOMA-IR), very low-density lipoprotein (VLDL), triglycerides, systolic blood pressure, and atherosclerotic cardiovascular disease risk estimate. These data support the use of GLP-1 agonists to counteract pathophysiological contributors to morbidity and premature mortality that may outweigh the risks of GLP-1 agonist-associated adverse effects among most people with HIV.

Although Lake et al. (2024) did not report extensively on adverse events, this single-arm clinical trial did report similar improvements to Eckard et al. (2024) regarding various markers, including intrahepatic triglyceride (IHTG), HOMA-IR, glucose (fasting), HbA1c, triglycerides, and alanine aminotransferase levels. Similarly, Lake et al. (2024) reported a decrease in the number of study participants with elevated alanine aminotransferase levels. Moreover, a substudy of the Lake et al. (2024) trial demonstrated the preservation of muscle function despite weight loss which included a significant loss of muscle (psoas) volume ($p < .001$); gait speed, which could be affected by reductions in psoas volume, actually demonstrated the potential to improve in this study (Ditzenberger et al., 2024). Despite little improvement in weight-related outcomes, the Bottanelli et al. (2023) study also noted duration-dependent improvements in HOMA-IR (median decrease of 3.3 over 36 months). These data not only suggest GLP-1 agonists offer anticipated metabolic benefits toward diabetes-related biomarkers (e.g., glucose, HOMA-IR) but also provide cardioprotective and hepatoprotective functions, while potentially preserving functional capacity and quality of life.

Moreover, no specific adverse event data were provided by Lake et al. (2024), but this study did note that most adverse events were grade 1 gastrointestinal symptoms, and all participants tolerated semaglutide at the provided dose (1 mg weekly). As such, it can be reasonably assumed that, of 49 study subjects, none discontinued the study due to adverse effects, further supporting the overall safety of GLP-1 agonists. This would indicate that just 14 of 328 (4.27%) study subjects with HIV discontinued GLP-1 use or changed to an alternative GLP-1 agonist due to intolerance or adverse effects. Thus, these data suggest that GLP-1 agonists may support pathophysiologic function even in the absence of weight-related changes.

Case Studies

In addition to the data above, which were collected and analyzed from studies involving 15 or more participants, five case studies were identified and included in the review for descriptive purposes. These cases provided preliminary evidence supporting the potential efficacy of GLP-1 agonists in people with HIV, despite the use of different drugs and the presence of distinct clinical scenarios (e.g., sepsis, diabetes). [Table A8](#) and [Figure A14](#) provide an overview of participant demographics (male and female, aged 40–62 years, various GLP-1 agonists) and summarize the key baseline characteristics and outcomes, respectively.

In alignment with the findings from cohort studies and clinical trials, these case studies demonstrated similar outcomes, supporting the overall efficacy of GLP-1 agonists in people with HIV for metabolic efficacy. Additionally, they revealed consistent trends, including strong correlations between weight loss and both baseline weight ($r = 0.988$) and follow-up period ($r = 0.867$). Some case studies also reported no notable disruptions to immunologic control. For instance, Oriot et al. (2011) observed sustained virologic suppression (<50 copies/mL) over 14 months, while Dardano et al. (2022) noted a marked improvement in viral load (29 copies/mL)

over three months. These observations support the conclusion that GLP-1 agonists do not negatively affect the efficacy of ART.

Adverse effects and other reported changes in various biomarkers also suggested the overall safety, or a positive benefit-to-risk ratio, of GLP-1 agonists in people with HIV. For instance, improvements were observed in urinary albumin-to-creatinine ratio, creatinine value, body fat percentage, waist circumference, HOMA-IR, liver enzymes, total cholesterol, HDL cholesterol, triglycerides, apnea-hypopnea index (related to sleep apnea), and overall quality of life. Moreover, these benefits were observed despite variance in GLP-1 agonist use, ARV use, including INSTIs and TAF, and various comorbidities.

Summary

This systematic review and meta-analysis aimed to address three primary research questions regarding the use of GLP-1 receptor agonists in people with HIV. The findings for each question are summarized below:

Research Question 1: Do GLP-1 receptor agonists produce significant metabolic outcomes (e.g., weight loss, HbA1c reduction) in people with HIV without affecting virologic response to ART?

Yes. GLP-1 receptor agonists were associated with statistically significant improvements in metabolic outcomes, including reductions in body weight (kg and %), BMI, and HbA1c. Effect sizes and post hoc power calculations further reinforced these findings with pooled data. However, these effects were not consistent across all subgroup analyses (e.g., semaglutide vs. varied GLP-1s) and dose strata, which warrants further consideration and evidence to support the use of alternative GLP-1 agonists. No consistent or clinically significant deterioration in CD4 count or viral suppression was observed overall, suggesting that GLP-1 agonists do not

compromise ART efficacy. While longitudinal immunologic data were sparse, the available evidence supports the metabolic benefits of GLP-1s without documented immunologic harm in the short term. As with any findings based on limited data, such as in this study, further research is needed to evaluate and confirm these outcomes.

Research Question 2: Are treatment outcomes influenced by the specific ART regimen used in combination with GLP-1 therapy?

No significant effect of ART, specifically INSTIs, on weight loss outcomes was observed based on the available data. While some literature suggests that INSTIs may contribute to weight gain, pooled data from this review indicated that GLP-1 agonists remain effective regardless of ART class. Correlation and linear modeling supported comparable metabolic benefits between INSTI and non-INSTI users, reinforcing the independence of GLP-1 efficacy from ART regimen. Of note, no clear data were available regarding the use of the antiretroviral tenofovir alafenamide, which also carries concerns related to weight gain. As such, these assumptions and statements are based solely on INSTI-related data and warrant further investigation in larger cohorts.

Research Question 3: Is the safety profile of GLP-1 receptor agonists in people with HIV consistent with that observed in the general population?

Yes, with minor caveats. Although adverse event reporting was limited, the available data suggest that GLP-1 receptor agonists are generally well tolerated in people with HIV. Gastrointestinal effects, such as nausea, constipation, and appetite changes, were the most commonly reported, mirroring those seen in the general population. No severe or life-threatening adverse events were identified, and discontinuation rates were low (~4.3%). The balance of

evidence supports a favorable safety profile, though further investigation into renal and gastrointestinal side effects is warranted, particularly in high-risk subpopulations.

Transitional Commentary

Collectively, the findings from this meta-analysis establish a foundation of support for the use of GLP-1 receptor agonists in the management of metabolic dysfunction among people with HIV. Not only do these agents demonstrate robust efficacy for weight reduction and glycemic control, but they also do so without compromising virologic suppression or triggering significant adverse outcomes. Importantly, the comparative outcomes between HIV-positive and HIV-negative populations, although limited, suggest that people with HIV derive comparable (if not superior) benefit from GLP-1 therapy.

However, these results must be interpreted within the broader clinical context, including the limitations posed by study heterogeneity, small sample sizes, and incomplete safety data. The consistent observation of benefit, despite such limitations, speaks to the *potential* value of GLP-1 agonists as an adjunctive tool in managing long-term cardiometabolic risk in people with HIV. Chapter 5 builds on these findings by discussing their clinical implications, potential mechanisms, and relevance to current guidelines. The chapter also proposes recommendations for future research, clinical practice, and policy development in light of the observed evidence gaps and emergent themes.

CHAPTER 5. DISCUSSION, IMPLICATIONS, RECOMMENDATIONS

Introduction

The purpose of this study was to evaluate the safety and efficacy of GLP-1 receptor agonists, particularly semaglutide, in people with HIV using a systematic review and meta-analysis of five studies, including clinical trials and retrospective observational cohorts. This investigation was conducted to address the knowledge gap regarding the metabolic, cardiovascular, and hepatic benefits of GLP-1 agents in this population, who have been (and continue to be) disproportionately affected by comorbid obesity, dyslipidemia, insulin resistance, and chronic inflammation. By examining the effects of semaglutide on weight loss, glycemic parameters, and adverse events, this study sought to determine whether GLP-1 agonists were a safe and effective treatment option for this medically complex population, particularly given documented concerns regarding weight-related changes with modern ART regimens.

Key findings indicated that semaglutide led to statistically significant and clinically meaningful improvements in weight loss, BMI, and glycemic control across most studies. Additionally, subgroup and bootstrap analyses demonstrated no statistically significant difference in weight loss outcomes by ART class (INSTI vs. non-INSTI), but did reveal significant differences by dose group, with subcutaneous doses of 1.7 to 2.4 mg producing statistically superior weight loss to oral doses ≥ 7 mg, even after adjusting for follow-up duration. Most adverse events were mild to moderate and aligned with the known safety profile of semaglutide (and other GLP-1 agonists), though modest increases in creatinine and gastrointestinal disturbances warrant further investigation.

Interpretation of the Findings

Weight Loss and Metabolic Outcomes

The results of this meta-analysis supported the preliminary conclusions drawn from both expert opinions and observational studies, which suggested that GLP-1 receptor agonists are effective for weight loss in people with HIV, demonstrated by a pooled average weight reduction of approximately 5.6 kg. This aligns with independent data from multiple cohorts (e.g., Eckard et al., 2024; Haidar et al., 2024) and case reports (e.g., Diamant & van Agtmael, 2012; Sheffield et al., 2007), all of which suggest a beneficial metabolic profile when GLP-1 agents were used alongside ART. However, by synthesizing data from both randomized and non-randomized studies, this analysis extends the current body of knowledge by providing a pooled estimate of effect size with statistical precision and confirmation of significance, even after accounting for sample heterogeneity and methodological limitations. Moreover, this meta-analysis pooled outcomes and associated effects from key parameters not included in all available studies (e.g., HbA1c, which was not provided by Bottanelli et al., 2023).

The observed trend of greater weight loss in individuals with higher baseline BMI is consistent with pharmacologic principles and clinical observations in the general population. However, this trend had not previously been statistically examined in people with HIV. Notably, given that weight changes can be directly induced by ART, it is plausible to consider the possible blunting of baseline BMI as a predictor for weight loss in this population. Correlational analyses conducted in this review (e.g., $r = -0.83$ between baseline BMI and weight loss) confirm the plausibility of prior anecdotal accounts and extend the literature by quantifying the relationship within a pooled sample of real-world and trial data.

Dosing Patterns and Pharmacologic Implications

One area where the current analysis meaningfully expanded previous literature was in the reporting and consideration of dosing practices. Several prior reviews (e.g., Hwang et al., 2024) speculated that dose optimization could be a limiting factor in real-world practice. The current analysis supported this concern: only two studies (Eckard et al., 2024; Lake et al., 2024) specified use of semaglutide 1.0 mg weekly, while others either omitted dose information or included pooled data for varied GLP-1 agents (e.g., liraglutide and dulaglutide), which may have been titrated inconsistently or prescribed below maximum efficacy thresholds. This dosing heterogeneity was particularly evident in retrospective studies, where variations in prescribing patterns could not be easily adjusted for.

This meta-analysis and systematic review provided evidence that, at comparable dosing, semaglutide, among all GLP-1 agonists, elicited metabolic outcomes similar to those observed in people without HIV over comparable durations. Moreover, given that research has demonstrated a clear dose-response relationship between GLP-1 agonists and metabolic outcomes, it is plausible to assume that even greater outcomes could be experienced by people with HIV at higher semaglutide doses (e.g., 1.7 or 2.4 mg). A bootstrapped analysis using raw data from Nguyen et al. (2024) supported this notion, albeit with limited data that warrants cautious interpretation.

Differences by GLP-1 Agent

The stratified subgroup analysis by GLP-1 receptor agonist showed the potential superiority of semaglutide over other agents, which affirmed preliminary observations noting variance in weight loss outcomes by GLP-1 agonist from Nguyen et al. (2024). In particular, researchers had previously speculated that dulaglutide is associated with lower weight loss

effectiveness, though dulaglutide itself did not elicit inferior results in this study statistically. Similarly, the use of tirzepatide and exenatide demonstrated interesting potential for significant changes to metabolic outcomes, but the lack of data continues to be a barrier to developing firm recommendations for their use.

Altogether, the pooled data suggested that GLP-1 agonists collectively yielded a significant ($p < .001$) meta-analytic effect, but not significant for semaglutide and varied GLP-1 agonist groups independently. Thus, the present findings provided data demonstrating conflicting metabolic outcomes among people with HIV when using different GLP-1 agonists. Importantly, the lack of comparable data between groups must be considered. Moreover, despite a lack of consistent outcomes, GLP-1 agonists such as exenatide and tirzepatide demonstrated interesting clinical potential; for example, these drugs exhibited lower limits (via 95% CI) of -47.63 kg and -12.11 kg, which exceeded that of any semaglutide dose (maximum lower limit of -9.5 kg). Further research should evaluate the effectiveness of alternative GLP-1 options in people with HIV.

Durability of Effects and Follow-Up Duration

The correlation analyses between follow-up duration and monthly treatment effects revealed a consistent attenuation in weight loss over time. These findings extend the literature by introducing a temporal lens to long-term efficacy. While expert reviews speculated on the sustainability of GLP-1 effects (e.g., Patoulas et al., 2024), no prior studies formally analyzed the decay or tapering of weight loss per unit time among this population. This observed attenuation, which was most apparent in monthly weight change or BMI change rates, showcased the diminishing returns of continued treatment and provided a foundation for future longitudinal modeling in people with HIV. Furthermore, these results created speculation

regarding the clinical expectations for weight loss persistence and the need for dose modulation or treatment cycling in longer-term care. The diminished long-term effects do not indicate that GLP-1 agonists are not appropriate for use in people with HIV, simply that their use may warrant more mindful prescription, implementation, and/or modification.

Baseline Weight and Attenuated Outcomes

Correlation analyses from the present study also supported the finding that individuals with lower baseline BMI experienced smaller absolute and relative weight loss. This finding aligns with general principles of weight physiology but had not been previously quantified in the HIV population using GLP-1 receptor agonists. Specifically, a strong inverse correlation was observed between baseline weight (kg) and absolute weight change ($r = -0.73$), suggesting a proportional ceiling effect. Similar outcomes were observed for baseline BMI and absolute weight change, further validating the effect ($r = -0.73$).

These results extend prior literature by emphasizing that baseline weight may moderate GLP-1 efficacy in this population. For instance, Bottanelli et al. (2023) reported an average BMI of 30 kg/m² and did not demonstrate statistically significant reductions in weight or BMI. The low efficacy in that cohort may reflect both agent choice (e.g., seven of 15 participants received dulaglutide) and a diminished capacity for further weight reduction at or near the overweight–obesity threshold. In contrast, larger effects were consistently observed in cohorts with baseline BMIs in the mid-to-upper 30s (e.g., Lake et al., 2024; Haidar et al., 2024). These observations support long-standing assumptions and extend the literature by placing quantitative boundaries around baseline characteristics that may predict treatment success in people with HIV. Importantly, these trends were more specific to weight-related metabolic outcomes and did not demonstrate the same degree of association with glycemic control via HbA1c. Thus, it is possible

that GLP-1 agonists continue to offer non-weight-related benefits in individuals with HIV with lower baseline weight or BMI.

ART Regimen Interactions

Although data were limited, the present analysis found no substantial differences in outcomes between individuals on INSTI-based versus non-INSTI-based ART regimens, consistent with the findings of Haidar et al. (2024). This outcome supports the view that GLP-1 agonists may be particularly valuable for people with HIV on an INSTI-based regimen, offering a therapeutic means to at least counteract ART-induced weight gain. Of note, these data did not offer specific insights into whether specific ARV drugs (e.g., BIC, DTG, TAF) result in blunted metabolic outcomes or other unique adverse effects. While evidence in this area remains sparse and observational, the meta-analytic comparison did not indicate a clinically meaningful difference in weight loss attributable to INSTI use, thereby confirming the maintained efficacy of GLP-1 agonists regardless of ART regimen (in pooled outcomes). However, given that this result was based on limited study-level data (two studies) and without the context of related implications (e.g., adverse effects, other ARVs in the regimen, etc.), caution is warranted when interpreting these findings from a clinical perspective.

Immunologic and Virologic Safety

This review found insufficient evidence to draw meta-analytic conclusions regarding immunologic (e.g., CD4 count) and virologic (e.g., HIV RNA) safety due to inconsistent and non-standardized reporting. Nevertheless, several individual studies (e.g., Lake et al., 2024; Noe et al., 2024) raised concerns regarding possible CD4 count suppression and HIV RNA elevation in a minority of cases. These mixed findings mirror concerns already noted in the literature and confirm the need for longer-term safety data with consistent laboratory monitoring. While the

present findings did not disconfirm safety, they highlight the lack of sufficiently powered or consistent evidence to draw definitive conclusions. Of note, this meta-analysis provided limited evidence suggesting that virologic control exerted minimal effect on GLP-1 efficacy. While these data also remain limited and should be interpreted with caution, they support the possibility that GLP-1 agonists may help mitigate weight gain (and ultimately weight-related comorbidities), even in individuals who remain viremic (e.g., untreated, drug-resistant HIV, virologic failure). Of note, such use would likely only be applicable if further evidence disproves any concerns related to CD4 count suppression.

Adverse Effects and Risk–Benefit Considerations

While the overall findings strongly supported the efficacy of GLP-1 receptor agonists in achieving weight and metabolic improvements in people with HIV, the safety profile remains incompletely defined. Safety concerns related to GLP-1 agonists echo those noted in previous literature, especially by Zino et al. (2023) and Noe et al. (2024), who reported modest yet potentially concerning reductions in CD4 cell counts and risks for gastrointestinal or pancreatic effects.

In this meta-analysis and systematic review, most studies did not report immunologic or virologic outcomes post intervention, thereby preventing a full risk–benefit assessment. Among those that did, findings were mixed. For example, Lake et al. (2024) observed viral rebound in three of 49 patients and a minor decrease in CD4 count, which confirmed concerns proposed by Noe et al. (2024). Importantly, the Lake et al. (2024) study did not establish causality or clinical consequences of these changes. These observations confirm ongoing concerns in the previous reviews and highlight a gap in current reporting standards. While such incidents were not observed in most studies, their associated ramifications (e.g., increasing the likelihood of HIV

transmission) warrant further investigation to determine factors that influence such immunologic or viral responses.

Nonetheless, serious adverse effects were rare in controlled trials. For instance, Eckard et al. (2024) reported only one grade 3–4 adverse event (elevated lipase) with no virologic failure, and three discontinuations due to adverse events. Interestingly, Lake et al. (2024) demonstrated that semaglutide may reduce lipase levels and decrease the number of participants with elevated lipase levels, showing potential clinical utility in this parameter. Moreover, discontinuation rates were low (<5%) based on data provided by applicable studies. Study authors frequently reported that GLP-1 agonists were generally well tolerated and offered clinical benefits that may outweigh the low-severity adverse effects documented by these agents. These findings supported the notion that short-term use of semaglutide in this population is generally well tolerated and aligned with safety findings from non-HIV populations, ultimately extending them into a new clinical domain. However, the long-term risk–benefit ratio remains unresolved due to the lack of standardized outcome reporting. Lastly, the magnitude of these findings and interpretations must be considered in light of the relatively low dose of semaglutide (1.0 mg) used in these studies and analyzed in this meta-analysis and systematic review.

Extension of Evidence Hierarchy

Prior to this analysis, most available studies were classified as low-tier evidence (case reports, uncontrolled observational studies). This systematic review and meta-analysis therefore extended the hierarchy of evidence for this research question by consolidating heterogeneous data into an interpretable summary of efficacy. Moreover, it supported clinical impressions from high-profile expert reviews while identifying quantifiable gaps in reporting, standardization, and subgroup analysis; gaps that can now inform future research.

Limitations of the Study

This study was subject to several limitations that should be considered when interpreting the findings. First and foremost, the total number of studies meeting eligibility criteria was relatively small ($n = 5$), three of which were observational in nature. As such, the analysis was constrained by a limited sample size at the study level, which reduced the statistical power and generalizability of pooled effect estimates. Moreover, the methodological quality of the included studies also varied, with most rated as having a moderate to high risk of bias due to concerns related to sample representativeness, incomplete outcome data, lack of blinding, or limited adjustment for confounders. There was also substantial variability in study designs, reporting practices, and outcome definitions. For instance, critical virologic and immunologic endpoints (e.g., HIV RNA viral load and CD4 count) were inconsistently reported or presented in non-comparable formats across studies, which precluded formal meta-analysis of these outcomes. Similarly, ART regimens were not described or provided consistently with associated outcomes, which limited the capacity to use certain ART regimens as a moderator of GLP-1 efficacy in this analysis. This lack of granularity limited the ability to fully evaluate potential interaction effects between GLP-1 agonist treatment and ART class.

Although efforts were made to identify all relevant studies, it is possible that some eligible reports were missed because the search was limited to PubMed and ClinicalTrials.gov during the initial phase. Additional gray literature searches or inclusion of databases, such as Embase, Scopus, or Web of Science, may have yielded additional data. For instance, a conference abstract was later identified, which provided a small sample of data ($n = 15$) among people with HIV using a variety of GLP-1 agonists (Lloyd et al., 2023). Such data may have

counteracted the limitations of the Bottanelli et al. (2023) study, particularly in the comparison of semaglutide versus varied GLP-1 usage and outcomes.

Numerous estimates and data transformations were required to harmonize reported outcomes for comparative analysis. These included the derivation of standard deviations from confidence intervals or ranges, conversion of change scores to absolute values, and estimation of weight loss in kilograms from percentage-based outcomes. While these techniques are well established in meta-analytic methodology, they introduce additional uncertainty and rely on assumptions that may not be uniformly valid across studies. The low study sample could plausibly amplify such uncertainty. The limited sample and the study designs implemented in this small sample also created software limitations for the analytic strategy. RevMan, which is well-suited for estimating variance in two-arm trials, could not accommodate mixed study designs or modeling effect moderators. GraphPad Prism lacked meta-analytic functionality altogether. Jamovi, though well-suited for generalized linear modeling and bootstrapping, did not support all forms of publication bias diagnostics (e.g., Egger's test), nor did it provide certain heterogeneity statistics (e.g., Q-statistic). As such, some inferential limitations remain.

In addition, analyses using raw data from the Nguyen et al. (2024) study relied on broader calculations. For instance, follow-up duration was estimated using the interval between recorded baseline and follow-up weight measurements. This approach yielded an average of 13.9 months, aligning closely with the 13.0 months reported by Nguyen et al. (2024). Alternate methods (e.g., using GLP-1 initiation to final outcome dates) produced comparable estimates. A few discrepancies were noted, such as final weight values recorded before GLP-1 initiation or differing final dates across outcomes, but these were limited in number and not expected to meaningfully impact findings. These challenges are common in retrospective chart reviews,

where data collection is targeted toward clinical needs rather than research goals. Such limitations further emphasize the value and need of prospective, controlled trials, which offer greater consistency and precision in outcome measurement.

Dosage-related analyses were blunted by the limited availability of dose-specific data across studies. Only two trials used standardized 1.0 mg semaglutide (subcutaneous), while observational cohorts included mixed regimens and, in some cases, oral GLP-1 formulations with dosing as high as 14 mg. Few subjects received higher weekly injectable doses (e.g., 2.4 mg), which are increasingly used in clinical practice. Furthermore, follow-up durations were short, typically six to eight months, and no prospective longitudinal studies were identified. Although some observational participants reported using GLP-1 receptor agonists for over three years, longitudinal data with structured follow-up and retention were not available. This significantly limited the ability to draw conclusions about long-term safety and efficacy.

Although the outcomes of this study appeared to favor GLP-1 use for metabolic outcomes in people with HIV in terms of weight and BMI, the ability to systematically review and analyze the influence of these drugs on lipodystrophies was limited. For example, the analyzed data did not account for the specific distribution of weight across the cohort via body fat percentage or other anthropometric measures. This was due to a lack of available data, although some data were identified that continued to support the use of GLP-1 agonists in this population for fat-specific weight loss and visceral fat loss. For instance, one early case study noted a decrease in body fat percentage of approximately 5.5% over 14 months (Oriot et al., 2011). Moreover, Eckard et al. (2024) provided substantial support for such outcomes, noting statistically significant improvements in waist circumference, total body fat, total limb fat, trunk fat, and abdominal adipose tissue (including total, subcutaneous, and visceral). Importantly, they

also noted no significant change in lean mass, suggesting that lean mass is mostly preserved during short-term (32 weeks) GLP-1 agonist use. Combined with the observed maintenance of gait performance by Ditzenberger et al. (2024), these data suggest that ARV-related lipodystrophy may be positively counteracted by GLP-1 use.

Lastly, despite the use of bootstrapping and covariate adjustment to improve analytic robustness, several model assumptions failed (e.g., Levene's test, Breusch–Pagan test), suggesting non-uniform variance across various parameters (e.g., dosage-specific outcomes) and some residual heteroscedasticity. While such findings may reflect the real-world variability of the underlying data, they warrant caution when interpreting inferential statistics. Overall, while the analytic approach was rigorous and adjusted where possible to account for data limitations, the collective impact of the small sample size, variability in outcome reporting, reliance on secondary data, and the short duration of available trials constrained the generalizability and reliability of conclusions regarding the long-term safety and efficacy of GLP-1 receptor agonists in people with HIV. Of note, the receipt of raw data from Nguyen et al. (2024) vastly improved the ability to provide secondary evidence for assumptions regarding analytic effects (e.g., effectiveness of different semaglutide doses).

Recommendations

The outcomes of this study outlined several areas in which further research is warranted to expand the evidence base to better inform the use of GLP-1 receptor agonists in people with HIV. Most notably, given the limitations of the current literature and the exploratory nature of this analysis, replication in larger, well-controlled clinical trials is strongly recommended. Future research should prioritize RCTs that include diverse populations of people with HIV and assess both short- and long-term metabolic and virologic outcomes. Importantly, population variants,

such as baseline values or genotypes, should be recorded and analyzed where feasible. This study suggested that GLP-associated weight loss is multifactorial, and ample research has noted significant genetic contributors to weight-related outcomes in people with HIV (Cindi et al., 2021; Griesel et al., 2021).

In addition to population-related differences, future research should conduct comparative analyses while isolating variables that may influence treatment response. For example, this meta-analysis demonstrated that stratified dosing studies are necessary to better understand dose-response effects in this population and to determine optimal regimens for individuals with varying clinical profiles. Similarly, future investigations should include extended follow-up durations to evaluate the sustainability of benefits and the emergence of adverse events over time, with considerations for the received GLP-1 dose. Given the duality of on-label GLP-1 use (i.e., for type 2 diabetes or obesity), studies should also evaluate the influence of GLP-1 agonists in these different populations while accounting for drug variations (ARV or GLP-1), baseline values (specifically weight and BMI), age, comorbidities, and lifestyle factors. During such trials, CD4 count and HIV viral load should be consistently reported using thresholds commonly noted in practice. For instance, it may be valuable to include people with HIV at any viral load (assuming presumed safety), but to stratify them into <50 copies/mL (generally undetectable, but possibly <20 copies/mL with certain tests), 50 to 200 copies/mL (detectable but suppressed), and >200 copies/mL (viremic; Panel, 2025).

Finally, the development of formal prescribing guidelines for GLP-1 use in people with HIV is warranted. Such guidelines should clearly define eligibility criteria for treatment candidacy, which may be informed by correlational markers such as baseline weight, glycemic control, diagnosed comorbidities, or prior treatment response or efforts. Given that this study has

demonstrated the potential for significant weight and non-weight-related outcomes, the benefits may exceed the risks of adverse effects in some subsets of people with HIV.

Although this dissertation does not offer prescriptive clinical guidance, several implications for practice can be cautiously inferred. Clinicians considering GLP-1 therapy should begin with a thorough review of the patient's health history, current ART regimen, and any prior metabolic interventions. Nonpharmacologic strategies, including diet and exercise, should remain first-line approaches and have long-standing evidentiary support for improved outcomes (Kubeyinje et al., 2023; Qin et al., 2024). For patients who have not experienced adequate improvement with lifestyle modification, or who decline to make such behavioral changes, shared decision-making that includes a personalized risk–benefit assessment is encouraged. Evidence has demonstrated that over 95% of people with HIV were aware of the benefits of exercise, yet less than 50% engaged in 30 minutes of daily physical activity (walking) or exercise (Hyle et al., 2021). Thus, the use of GLP-1 agonists could be warranted in some scenarios when other interventions are avoided or ineffective and the risks of no intervention (e.g., accumulating morbidity) outweigh those of intervention (e.g., adverse effects, with limited data). If GLP-1 therapy is initiated, dosing should be individualized and titrated to evaluate tolerability, and patients should be monitored closely for metabolic outcomes (including a comprehensive metabolic panel), adverse effects, and any changes in HIV-related biomarkers. Periodic reassessment of treatment effectiveness and necessity is advised to ensure long-term safety and clinical value. Unlike ART, the use of GLP-1 agonists can be discontinued if a patient meets a desired clinical threshold (e.g., BMI <30).

Conclusion

This meta-analysis is the first to systematically evaluate the safety and effectiveness of GLP-1 receptor agonists in people with HIV, synthesizing data across six studies and four primary outcomes. By aggregating real-world and clinical trial data, the analysis offers a more precise estimate of treatment effects—most notably, consistent and clinically meaningful reductions in weight, BMI, and HbA1c. The strongest effects were observed with semaglutide, which also had the most robust and consistently reported data.

The use of subgroup, sensitivity, and correlation analyses enhanced the interpretive value of this review. Correlations with baseline BMI and follow-up duration revealed important trends, such as diminished weight loss over time and greater responsiveness among those with higher initial adiposity. Risk-of-bias assessments further contextualized these findings, revealing limitations in study design and reporting, particularly among retrospective cohorts. Despite these limitations, the overall evidence supports the continued investigation and use of GLP-1 receptor agonists in this population.

This study addresses a major gap in the HIV and metabolic health literature by advancing the evidence tier from scattered case studies and observational reports to a structured, quantitative synthesis. It provides a high-yield reference for clinicians, researchers, and policymakers seeking to improve care for people with HIV, particularly those experiencing ART-associated weight gain or metabolic dysfunction. Future randomized studies with longer follow-up, varied doses with dose-specific outcomes, and detailed monitoring of adverse effects as well as virologic and immunologic control, are warranted to build on these findings.

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APPENDIX A. TABLES, FIGURES, AND ITEMS

Table A1

History of Key Antiretroviral Drugs

Drug name	Drug class	Year FDA approved
Zidovudine	Nucleoside Reverse Transcriptase Inhibitor	1987
Didanosine	Nucleoside Reverse Transcriptase Inhibitor	1991
Zalcitabine	Nucleoside Reverse Transcriptase Inhibitor	1992
Stavudine	Nucleoside Reverse Transcriptase Inhibitor	1994
Lamivudine	Nucleoside Reverse Transcriptase Inhibitor	1995
Saquinavir	Protease Inhibitor	1995
Ritonavir	Protease Inhibitor	1996
Indinavir	Protease Inhibitor	1996
Nevirapine	Non-Nucleoside Reverse Transcriptase Inhibitor	1996
Delavirdine	Non-Nucleoside Reverse Transcriptase Inhibitor	1997
Nelfinavir	Protease Inhibitor	1997
Efavirenz	Non-Nucleoside Reverse Transcriptase Inhibitor	1998
Abacavir	Nucleoside Reverse Transcriptase Inhibitor	1998
Amprenavir	Protease Inhibitor	1999
Lopinavir/Ritonavir	Protease Inhibitor	2000
Tenofovir Disoproxil Fumarate*	Nucleotide Reverse Transcriptase Inhibitor	2001
Atazanavir	Protease Inhibitor	2003
Enfuvirtide	Fusion Inhibitor	2003
Fosamprenavir	Protease Inhibitor	2003
Emtricitabine	Nucleoside Reverse Transcriptase Inhibitor	2003
Tipranavir	Protease Inhibitor	2005
Darunavir	Protease Inhibitor	2006
Maraviroc	CCR5 Antagonist	2007
Raltegravir	Integrase Strand Transfer Inhibitor	2007

Drug name	Drug class	Year FDA approved
Etravirine	Non-Nucleoside Reverse Transcriptase Inhibitor	2008
Rilpivirine	Non-Nucleoside Reverse Transcriptase Inhibitor	2011
Elvitegravir	Integrase Strand Transfer Inhibitor	2012
Dolutegravir	Integrase Strand Transfer Inhibitor	2013
Cobicistat	Pharmacokinetic Enhancer	2014
Tenofovir Alafenamide	Nucleoside Reverse Transcriptase Inhibitor	2016
Doravirine	Non-Nucleoside Reverse Transcriptase Inhibitor	2018
Ibalizumab-uiyk	Post-Attachment HIV-1 Inhibitor	2018
Bictegravir	Integrase Strand Transfer Inhibitor	2018
Fostemsavir	Attachment Inhibitor	2020
Cabotegravir	Integrase Strand Transfer Inhibitor	2021
Lenacapavir	Capsid Inhibitor	2022

*Tenofovir disoproxil fumarate and tenofovir alafenamide are prodrugs of tenofovir and may be used to treat chronic hepatitis B infection.

Table A2*Overview of Reviewed PubMed Studies*

Study	Authors	Year	Type	Key Information
Are glucagon-like peptide 1 receptor agonists effective in decreasing body weight and body mass index in people living with diabetes and HIV?	Bottanelli, M., et al.	2024	Retrospective Single-Cohort Study	Early data suggests limited effects on weight loss, BMI, and blood glucose in diabetics with HIV when using dulaglutide. Lower weight loss trend observed compared to non-diabetics with GLP-1 use.
Blockbuster obesity drug leads to better health in people with HIV	Lenharo, M.	2024	News Article	Highlights early benefits of GLP-1 agonists, including improvements in weight, liver health, and reduced inflammation.
CROI 2024: Metabolic and Other Complications of HIV Infection	Sarkar, S. & Brown, T.	2024	Review	Summarizes presentations from the 2024 Conference on Retroviruses and Opportunistic Infections.
Effects of Semaglutide on Muscle Structure and Function in the SLIM LIVER Study	Ditzenberger, G., et al.	2024	Secondary Analysis, Single Arm of SLIM LIVER	Study reported semaglutide-related weight loss that included muscular atrophy with preserved neuromuscular function.
Glucagon-like Peptide 1 Receptor Agonists Promote Weight Loss Among People With HIV	Nguyen, Q., et al.	2024	Retrospective Single-Cohort Study	Demonstrates weight loss, reduced BMI, and HbA1c improvements. Noted dose-duration-response and enhanced results with tirzepatide compared to other GLP-1 agonists.
Immunological alterations with GLP-1 agonists in people living with HIV	Noe, S., et al.	2024	Retrospective Single-Cohort Study	Noted that early data shows an initial decline in CD4 counts post-GLP1 agonist administration in people with HIV.

Study	Authors	Year	Type	Key Information
Is the GLP-1 receptor agonist, semaglutide, a good option for weight loss in persons with HIV?	Lee, D. & Capeau, J.	2024	Editorial	Highlights early research success with GLP-1 agonists supporting weight loss, including in PWH who take INSTIs.
Once-weekly semaglutide in people with HIV-associated lipohypertrophy: a randomised, double-blind, placebo-controlled phase 2b single-centre clinical trial	Eckard, A., et al.	2024	Phase 2b RCT	Semaglutide use demonstrated reductions in abdominal fat, visceral adipose tissue, and total body fat. Elevated lipase and cholelithiasis noted as adverse effects.
Semaglutide in people with HIV-associated lipohypertrophy	Hwang, J., et al.	2024	Review	Confirms positive effects of semaglutide with minimal adverse events at standard doses.
The Effect of Open-Label Semaglutide on Metabolic Dysfunction-Associated Steatotic Liver Disease in People With HIV	Lake, J., et al.	2024	Phase 2B Single Group Open-Label Trial (SLIM LIVER ORIGINAL)	Semaglutide improved intrahepatic triglycerides and metabolic dysfunction markers. Mild GI adverse effects reported.
Unraveling the safety and efficacy of semaglutide for people living with HIV and metabolic comorbidities	Patoulis, D., et al.	2024	Review	Review showing positive benefits of semaglutide demonstrated in initial studies but called for further research.
Weighing In: Glucagon-Like Peptide-1 Receptor Agonism for Persons With HIV	Thomas, T. & Srinivasa, S.	2024	Review	Overview of GLP-1 agonist research for HIV populations, but lacks detailed literature consolidation for ART regimens or subpopulations.

Study	Authors	Year	Type	Key Information
Weight loss associated with semaglutide treatment among people with HIV	Haidar, L., et al.	2024	Observational Cohort Study	Notable weight loss and reductions in HbA1c levels reported after one year of treatment.
GLP-1 agonists for people living with HIV and obesity, is there a potential?	Zino, L., et al.	2023	Review	Discusses the potential of liraglutide and semaglutide use in PWH based on recent FDA guidelines; highlights drug interactions and monitoring concerns.
HIV and obesity: updates in management strategies	Parra-Rodriguez, L. & O'Halloran, J.	2023	Review	Reviews GLP-1 agonists for HIV patients, focusing on benefits and weight gain concerns with new ART regimens.
An enhanced participant information leaflet and multimedia intervention to improve the quality of informed consent to a randomised clinical trial enrolling people living with HIV and obesity: a protocol for a Study Within A Trial (SWAT)	O'Sullivan, L., et al.	2022	Prospective, Multi-Center, RCT	Protocol for SWIFT study recruitment aimed at improving informed consent.
Efficacy of Dulaglutide in a Patient With Type 2 Diabetes, High Cardiovascular Risk, and HIV: A Case Report	Dardano, A., et al.	2022	Single Case Study	Describes a 55-year-old woman with HIV and type 2 diabetes. Observed improvements in weight loss and glycemic control after dulaglutide treatment.
Under-utilisation of cardioprotective glucose-lowering medication in diabetics living with HIV	Butale, B., et al.	2022	Retrospective Single-Cohort study	Highlights low prescription rates for GLP-1 agonists and related drugs for diabetics with HIV, potentially due to limited awareness of interactions.

Study	Authors	Year	Type	Key Information
Pharmacist Intervention Lowers HgbA1c in Diabetic Patients Regardless of HIV Status	Nelson, N., et al.	2021	Retrospective Observational Cohort Study	Demonstrates effectiveness of pharmacist intervention on GLP-1 use in reducing HbA1c for diabetics, with some increased hypoglycemia risk for those with HIV.
Glucagon-like peptide-1 receptor agonists may ameliorate the metabolic adverse effect associated with antiretroviral therapy	Culha, M., et al.	2016	Review	Suggests that GLP-1 agonists may reduce ART-associated weight gain, but more research is needed.
Liraglutide treatment in a patient with HIV, type 2 diabetes and sleep apnoea-hypopnoea syndrome	Garcia de Lucas, M., et al.	2014	Single Case Study	Case study of a 62-year-old male reporting significant weight loss and improved glycemic control with liraglutide.
Liraglutide treatment in a patient with HIV and uncontrolled insulin-treated type 2 diabetes	Diamant, M. & van Agtmael, M.	2012	Single Case Study	Case study of a 57-year-old male reporting weight loss, improved triglycerides, and cholesterol while maintaining virologic suppression.
Exenatide improves weight loss insulin sensitivity and β -cell function following administration to a type 2 diabetic HIV patient on antiretroviral therapy	Oriot, P., et al.	2011	Single Case Study	Describes a 47-year-old patient achieving weight loss, improved HbA1c, and increased insulin sensitivity with exenatide.
Off-label use of exenatide for the management of insulin-resistant type 1 diabetes mellitus in an obese	Sheffield, C., et al.	2007	Single Case Study	Case of a 40-year-old male who achieved a 20% reduction in body weight, improved HbA1c, and reported enhanced quality of life.

Study	Authors	Year	Type	Key Information
patient with human immunodeficiency virus infection				

Item A1. Information Request

Subject: Request for Additional Data for Systematic Review and Meta-Analysis on GLP-1 Receptor Agonists in ART-Experienced People with HIV

Dear [Author's Name],

I hope this message finds you well. My name is Thomas Barnett, and I am a doctoral candidate (DHSc) at Keiser University, currently working on my dissertation. I am conducting a systematic review and meta-analysis on the use of GLP-1 receptor agonists in ART-experienced people with HIV, given the growing interest and popularity of this topic.

Given the limited availability of comprehensive data in this area, I am reaching out to authors of key studies (observational cohort studies and RCTs) to request any additional data that could be valuable in identifying trends and outcomes that have yet to be formally referenced. For instance, most of these studies only provide class-specific data for ARVs, rather than ARV-specific data; my goal is to review both (if applicable) to deduct the most refined conclusions possible.

I have identified your study, [Title of the Study], as a crucial contribution to this field, and I believe that any additional data you could provide would greatly enhance the comprehensiveness of this analysis. Data of interest include, but are not limited to, detailed patient demographics, specific treatment regimens, adherence rates, and any observed clinical outcomes.

Your assistance would be instrumental in advancing our understanding of the effects of GLP-1 receptor agonists in this population and could significantly contribute to the scientific community's knowledge base. I am more than willing to discuss my research further and address any questions you may have regarding this request.

In alignment with ethical guidelines and data protection standards, please ensure that any shared data is fully de-identified and **does not** contain personally identifiable information. All received data will be securely stored and handled in strict compliance with institutional and regulatory confidentiality protocols.

Thank you in advance for considering my request. I greatly appreciate your time and assistance.

Best,

Thomas Barnett
DHSc Student, HIV Clinical Guidelines Editor
Keiser University
t.barnett3@student.keiseruniversity.edu

1. Estimating Mean and Standard Deviation from Median and IQR

Used when studies reported median and interquartile range (IQR), but not mean or SD:

- **Estimated Mean** = $(Q1 + \text{Median} + Q3) / 3$
 - **Estimated SD** = $(Q3 - Q1) / 1.35$
-

2. Estimating Standard Deviation from Mean, 95% Confidence Interval, and Sample Size

Used when studies reported mean, 95% CI, and sample size:

- **Standard Error (SE)** = $(\text{Upper CI} - \text{Lower CI}) / 3.92$
- **Estimated SD** = $SE \times \sqrt{n}$

Note: These calculations were performed using RevMan, which automates this estimation.

3. Estimating BMI Change from Weight Change (when height is known or estimated)

Used when BMI change was not reported but baseline BMI and weight were:

- **Height (in meters)** = $\sqrt{(\text{Baseline Weight} / \text{Baseline BMI})}$
 - **Mean BMI Change** = $\text{Mean Weight Change} / (\text{Height}^2)$
 - **SD of BMI Change** = $\text{SD of Weight Change} / (\text{Height}^2)$
-

4. Estimating Percent Change in Body Weight

Used when only absolute weight change and baseline weight were available:

- **% Change in Weight** = $(\text{Change in Weight} / \text{Baseline Weight}) \times 100$
-

5. Estimating SD of Percent Change in Weight

- **SD (%)** = $(\text{SD of Absolute Weight Change} / \text{Baseline Weight}) \times 100$

Item A3. Risk of Bias Assessment

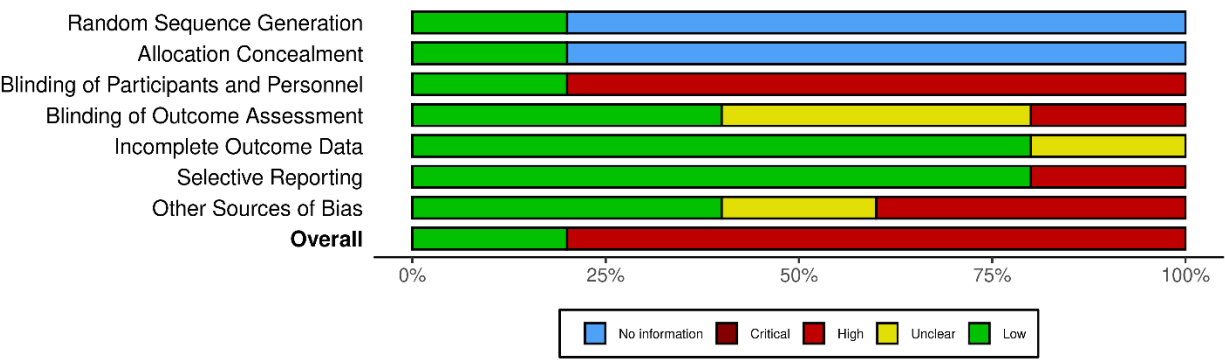
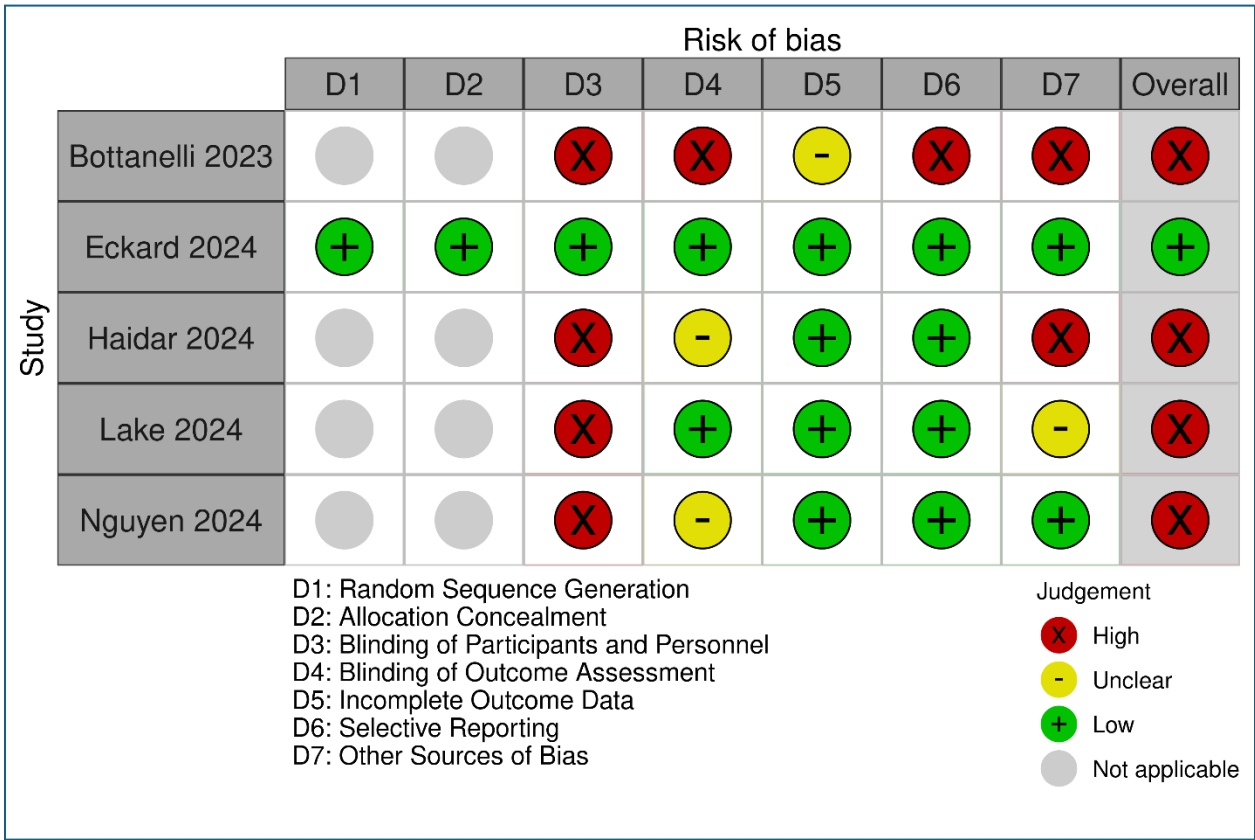


Figure A1

PRISMA Study Selection Flowchart

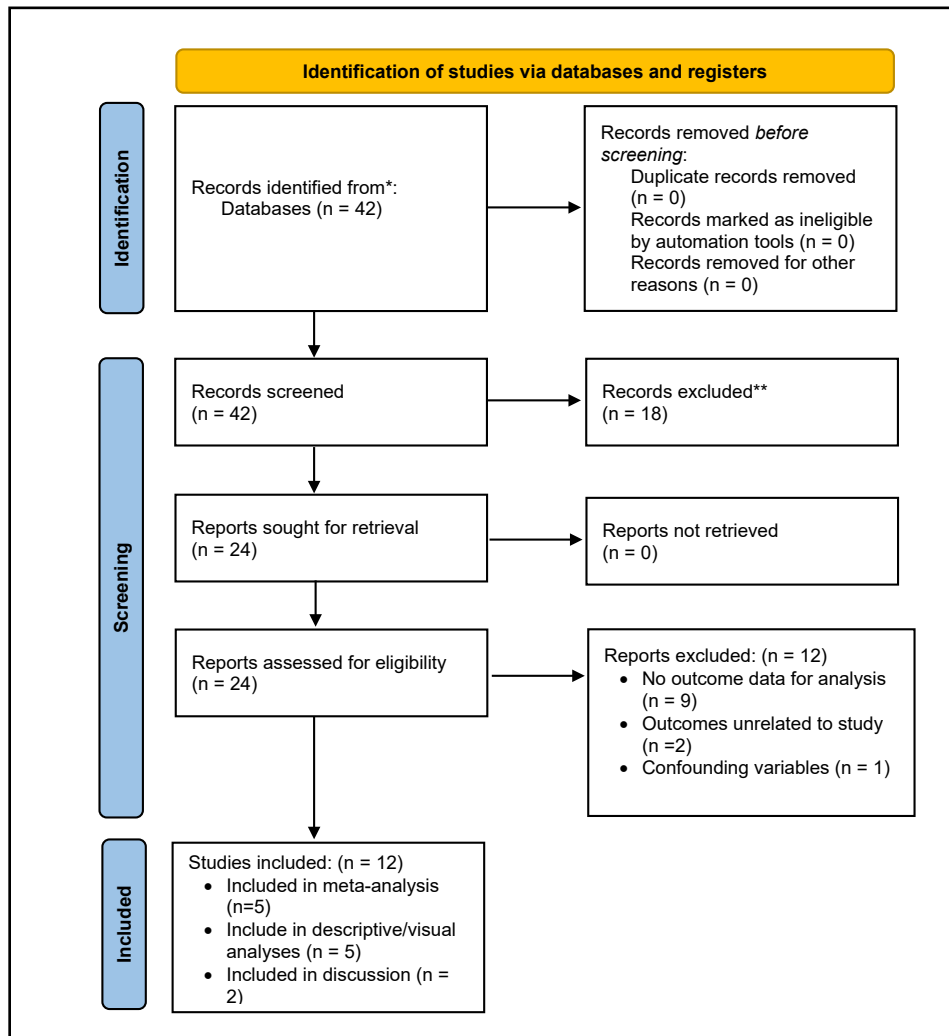


Table A3*Descriptive Characteristics of Included Studies*

Study	Study Type	GLP-1	Sample (HIV Only)	Mean Age	Male	Female	Transgender
Bottanelli 2023	Retrospective	Varied	15	58.1	13	2	0
Eckard 2024	RCT	Semaglutide	54	50	38	16	0
Haidar 2024	Retrospective	Semaglutide	222	52.8	166	56	0
Lake 2024	Singe-Arm Clinical Trial	Semaglutide	49	50.7	28	18	3
Nguyen 2024	Retrospective	Varied	227	54.1	186	41	0

Figure A2

Forest Plot: Meta-Analysis BMI Change

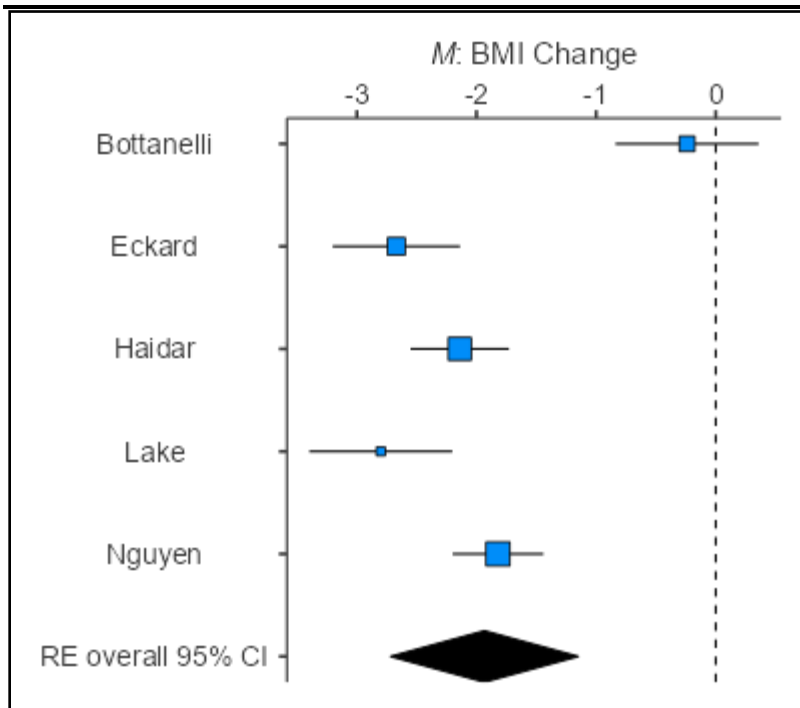


Figure A3

Forest Plot: Meta-Analysis Monthly Weight Change (kg)

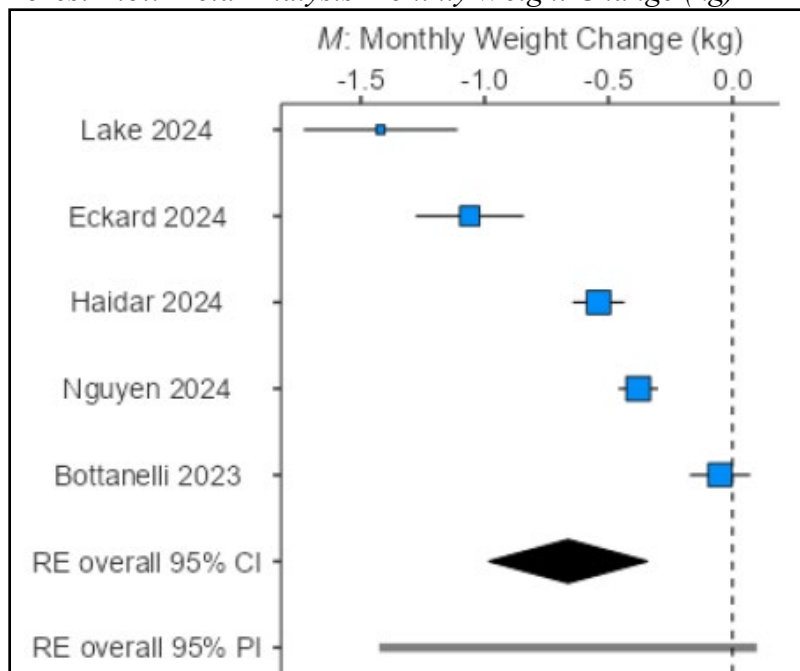


Figure A4

Post Hoc Power Analysis: Random Effects

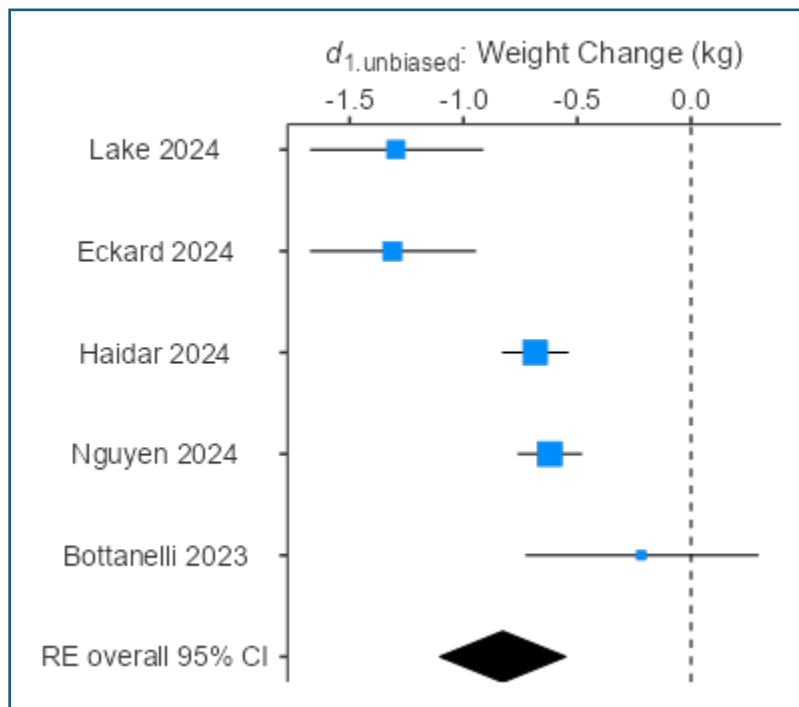


Figure A5

Post Hoc Power Analysis: Fixed Effects

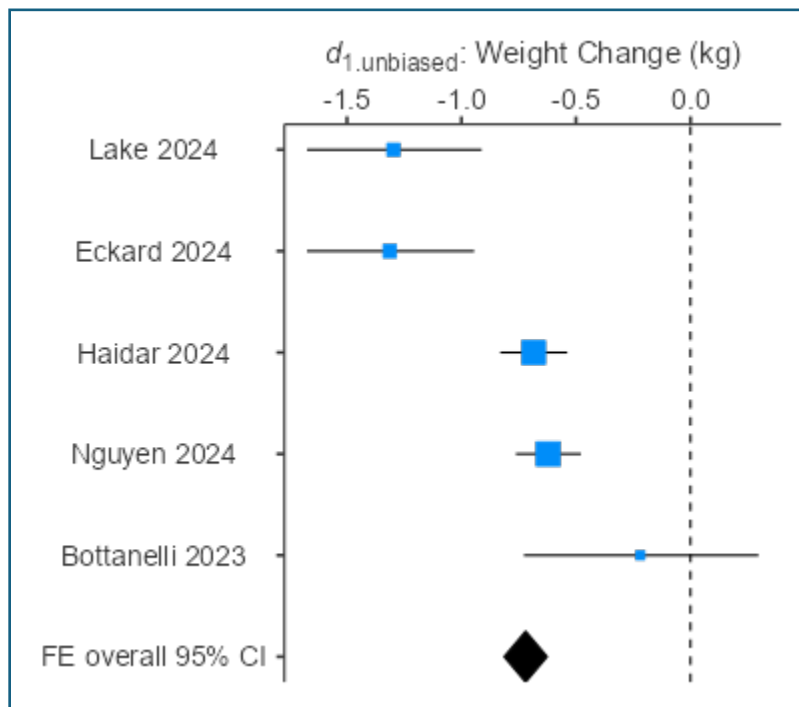


Figure A6

Effect Analysis of Semaglutide Versus Varied GLP-1 on BMI

Moderator Analysis							
Effect	Moderator	Level	M	95% CI		SE	p, two tailed
				LL	UL		
Change in BMI	GLP-1 Use	Varied GLP-1	-1.06	-2.073	-0.0473	0.517	0.040
		Semaglutide	-2.53	-3.362	-1.6924	0.426	<.001
		Varied GLP-1 – Semaglutide	1.47	0.155	2.7796	0.670	0.028

Note. Estimate is based on a random effects (RE) model.

Figure A7

Meta-Analysis Weight Loss by GLP-1

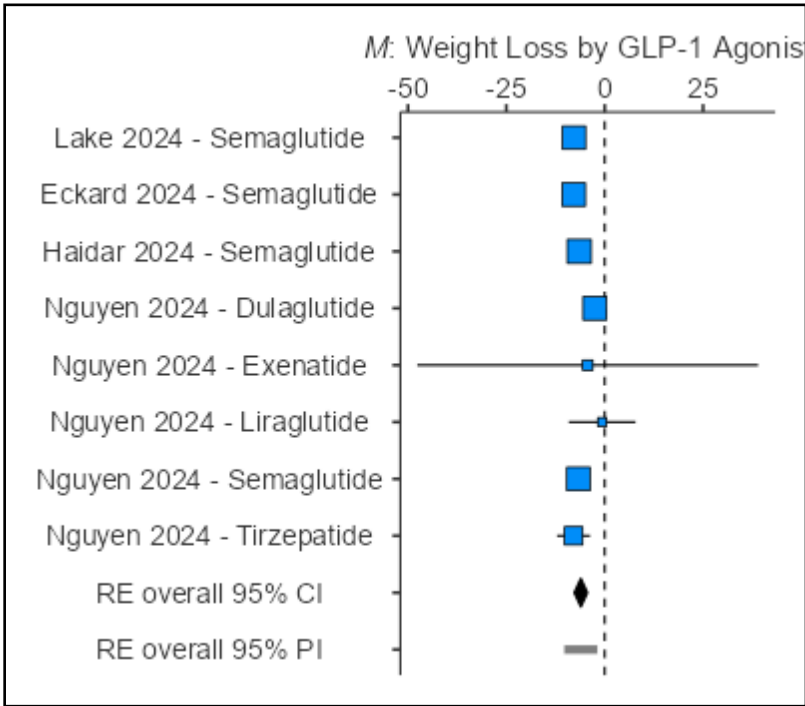


Table A4*GLP-1 Agonist Use and Outcomes of Included Studies*

Study	Dose	Drug	Follow-Up (Months)	Mean Weight Loss	SD Weight Loss
Lake 2024	1 mg	Semaglutide	5.5	-7.8	5.92
Eckard 2024*	1 mg	Semaglutide	7.4	-7.87	5.91
Haidar 2024	Varied	Semaglutide	12	-6.47	9.42
Nguyen 2024	Varied	Varied	13.9	-5.29	8.49
Bottanelli 2023	Varied	Varied	12	-0.6	2.59

***Note:** The Eckard et al. (2024) study was conducted over 32 weeks, but the semaglutide dose was titrated for 8 weeks before administering the full 1.0 mg dose for the remaining 24 weeks.

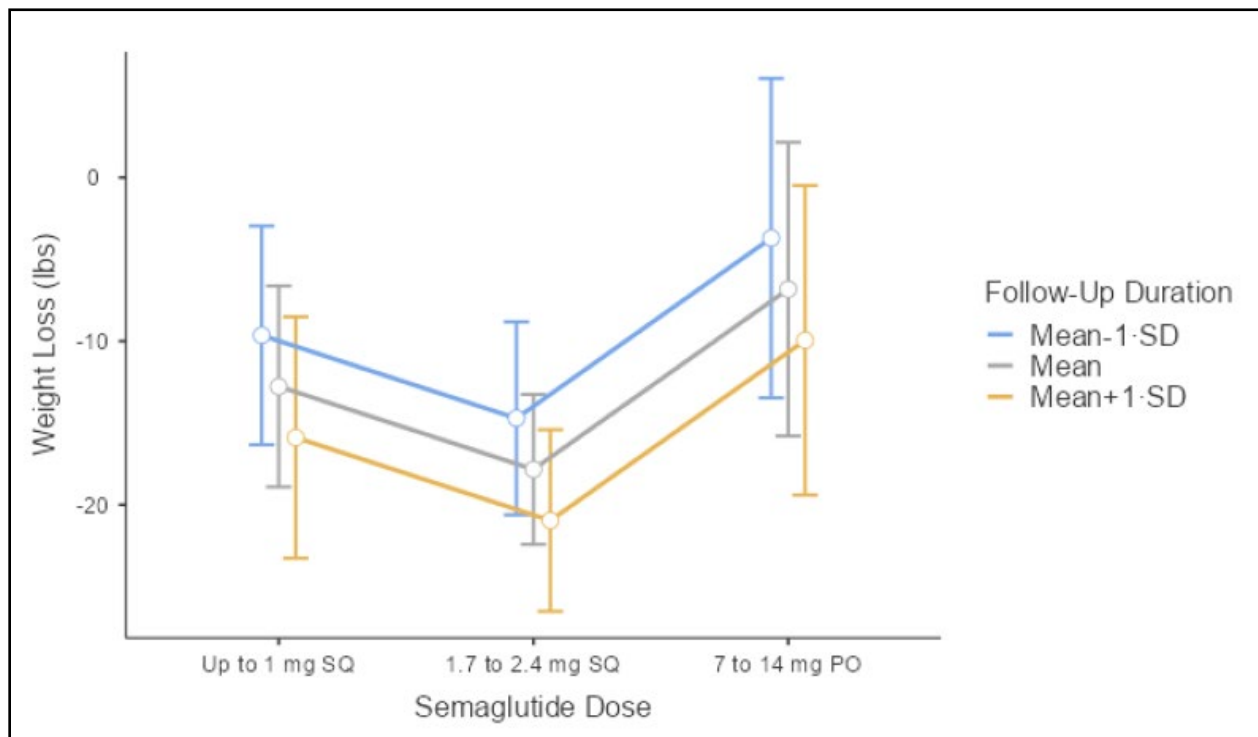
Figure A8*Weight Loss (lbs) by Semaglutide Dose and Follow-Up*

Figure A9

Correlation: Weight Change (kg) Versus Mean Baseline Weight

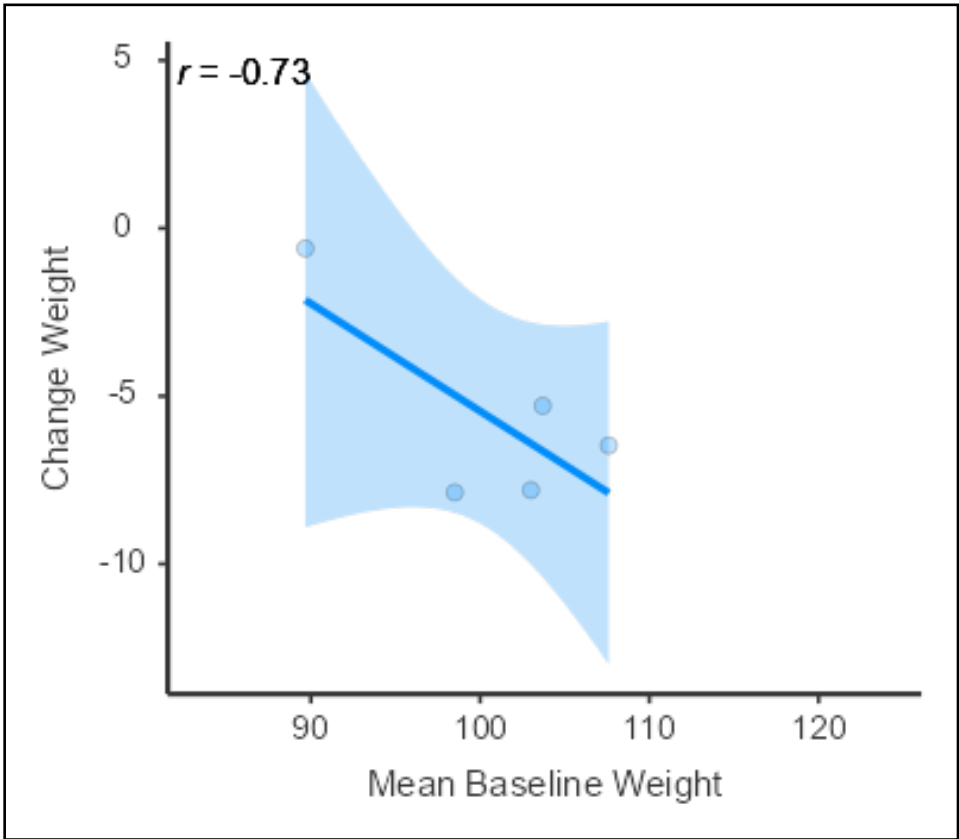


Table A5

Summary of CD4 and Viral Load Reporting

Study	Baseline CD4 (mean ± SD)	VL Format	Baseline VL	Change in CD4 reported?	Change in VL reported?
Bottanelli (2023)	818 ± 105	% <50 copies/mL	15/15 (100%)	No	No
Eckard (2024)	763 ± 482.2	VL <400 copies/mL	53/54 (98.1%)	No	Yes (54/54; 100%)
Haidar (2024)	796 ± 392	% <50 copies/mL	198/222 (89.2%)	No	No
Lake (2024)	762 ± 340	% <50 copies/mL	49/49 (100%)	Yes (-14 cells/mm ³ [95% CI. -81.1, 53.1])	Yes (46/49; 93.9%)
Nguyen (2024)	743.8 ± 357.9	% <50 copies/mL	199/225 (88.4%)	No	No

Table A6

Comparison of Studies Among People With and Without HIV Using Comparable Methodology

Study	Duration	Sample	Mean Weight Change (kg)
Sustain 1	30 weeks	130	-4.5
Sustain 2	30 weeks	360	-5.2
Sustain 3	30 weeks	131	-6.4
Sustain Forte	40 weeks	471	-6
Eckard 2024	32 weeks	54	-7.87
Lake 2024	24 weeks	49	-7.8

Figure A10

Comparison of Weight Loss (kg) Outcomes From Studies Among People With and Without HIV

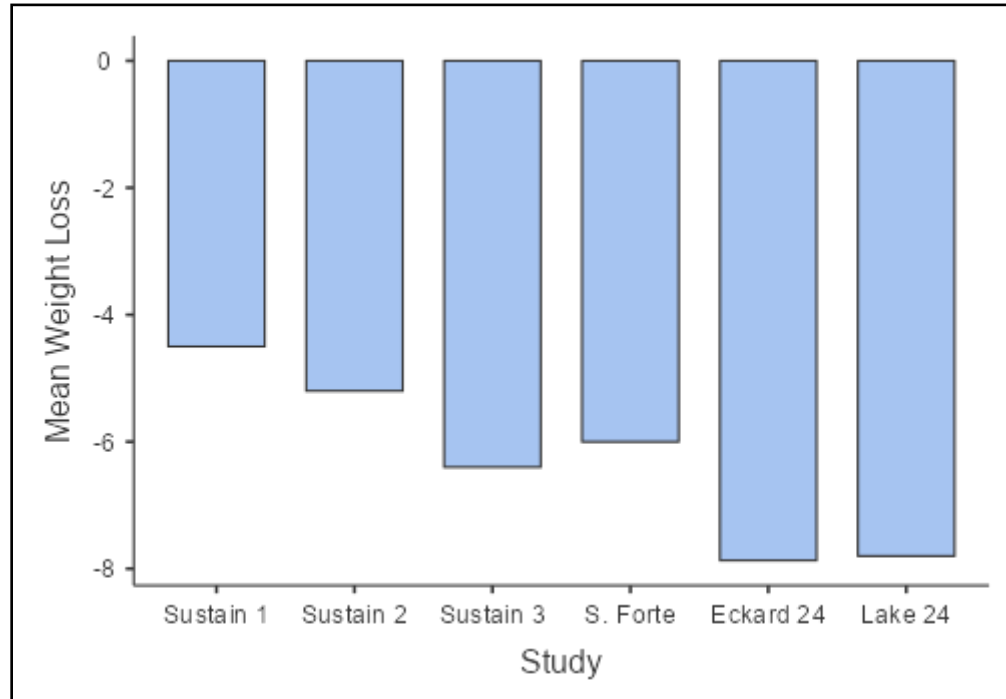


Figure A11

Weight Loss With and Without INSTIs

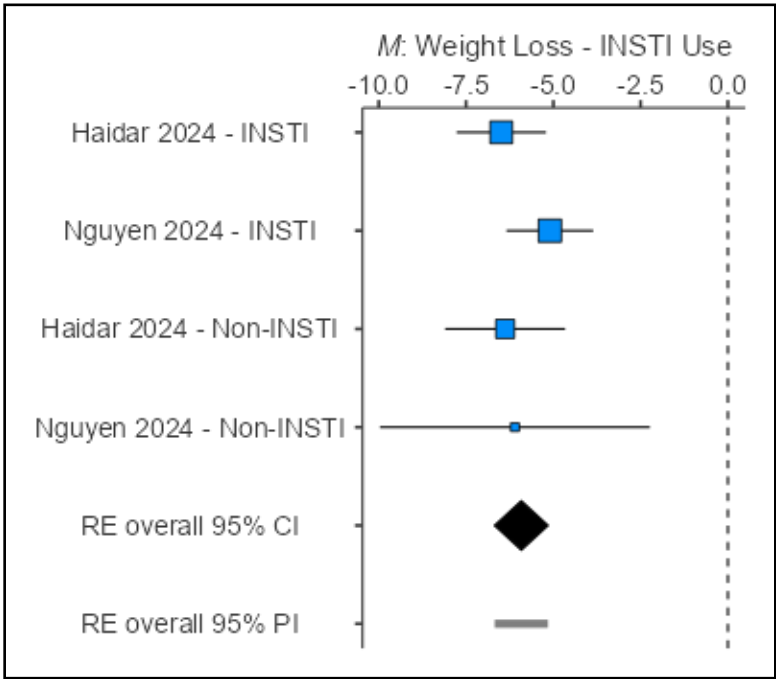


Figure A12

Correlation Between Weight Change (kg) and % of Subjects on INSTI-Based ART Regimens

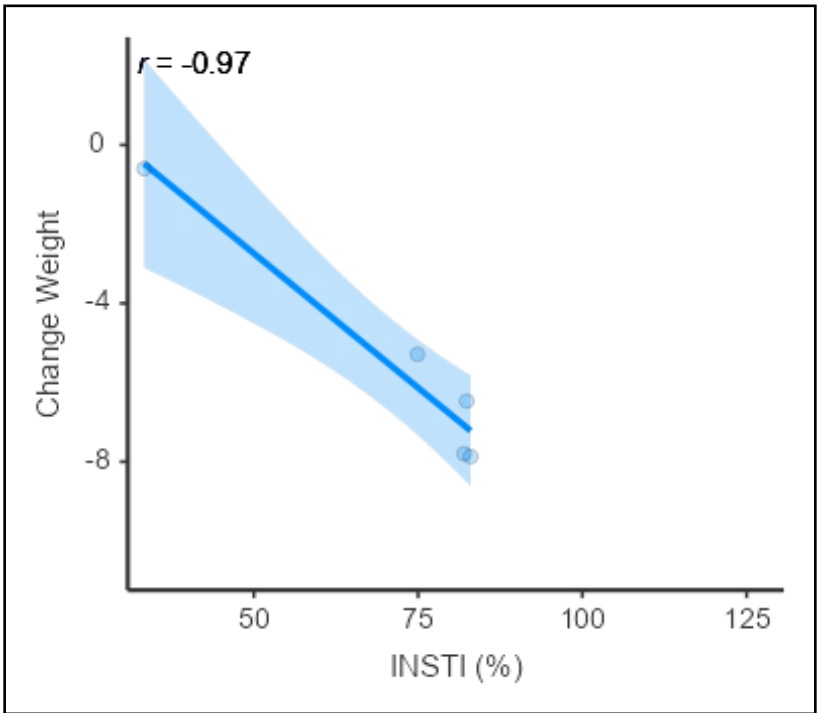


Figure A13*Estimates of INSTI-Related Influence on Weight Loss (kg) Outcomes*

Parameter Estimates (Coefficients)									
Names	Effect	Estimate	SE	95% Confidence Intervals		β	df	t	p
				Lower	Upper				
(Intercept)	(Intercept)	-12.229	2.223	-16.723	-8.153	-0.039	195	-5.502	<.001
ARV Class1	INSTI - Non-INSTI	1.999	4.445	-6.248	10.909	0.108	195	0.450	0.653

Note. Inferential tests and p-values of the effects are adjusted for heteroschedasticity.

Figure A14*Overview of Baseline Characteristics and Key Outcomes From Case Studies*

Descriptives							
Descriptives							
Study	Follow-up Period (months)	Baseline Weight (kg)	Baseline BMI	Change Weight (kg)	Change BMI	Change Weight (%)	Change HbA1c (%)
Dardano 2022	3.00	48.5	20.2	-1.30	-1.30	-2.70	-1.90
de Lucas 2014	24.0	118	41.3	-16.0	-5.60	-13.6	-1.20
Diamont 2012	7.00	116	35.1	-8.00	-2.50	-6.90	-1.30
Oriot 2011	14.0	107	32.6	-15.0	-4.60	-14.0	-1.10
Sheffield 2007	11.0	123	42.3	-24.0	-8.40	-19.5	-1.40

Table A7*Notable Adverse Effects From Eckard et al. (2024)*

Adverse Event	Study-Related				Non-Study-Related			
	Semaglutide Group	Placebo Group	Risk Difference (95% CI)	Risk Classification	Semaglutide Group	Placebo Group	Risk Difference (95% CI)	Risk Classification
Elevated lipase (any)	4 (7%)	2 (4%)	0.0370 (-0.0594 to 0.1309)	Low	8 (15%)	3 (6%)	0.0926 (-0.0282 to 0.2068)	Moderate
Elevated creatinine	1 (2%)	1 (2%)	0.0000 (-0.0687 to 0.0687)	Low	24 (44%)	13 (24%)	0.2037 (0.0238 to 0.3691)	High
Elevated AST	N/A	N/A	N/A	N/A	3 (6%)	4 (7%)	-0.0185 (-0.1185 to 0.0828)	Low
Elevated glucose	N/A	N/A	N/A	N/A	25 (46%)	39 (72%)	-0.2592 (-0.4262 to -0.0738)	High
Any gastrointestinal disorder	18 (33%)	15 (28%)	0.0556 (-0.1178 to 0.2250)	Moderate	35 (65%)	27 (50%)	0.1481 (-0.0385 to 0.3242)	High
Nausea	6 (11%)	4 (7%)	0.0370 (-0.0787 to 0.1501)	Low	15 (28%)	7 (13%)	0.1481 (-0.0068 to 0.2925)	High
Vomiting	1 (2%)	0 (0%)	0.0185 (-0.0419 to 0.0776)	Low	8 (15%)	3 (6%)	0.0926 (-0.0282 to 0.2068)	Moderate
Diarrhea or loose stools	0 (0%)	7 (13%)	-0.1296 (-0.2230 to -0.0270)	High	7 (13%)	10 (19%)	-0.0556 (-0.1922 to 0.0851)	Moderate
Constipation or irregular BM	2 (4%)	2 (4%)	0.0000 (-0.0834 to 0.0834)	Low	16 (30%)	5 (9%)	0.2037 (0.0513 to 0.3416)	High
Dyspepsia	1 (2%)	2 (4%)	-0.0185 (-0.0943 to 0.0586)	Low	11 (20%)	0 (0%)	0.2037 (0.0835 to 0.3094)	High
Cholelithiasis	2 (4%)	0 (0%)	0.0370 (-0.0327 to 0.1041)	Low	N/A	N/A	N/A	N/A
Appetite Changes	7 (13%)	1 (2%)	0.1111 (0.0034 to 0.2109)	High	8 (15%)	4 (7%)	0.0741 (-0.0504 to 0.1932)	High
Discontinuations*	4 (7%)	1 (2%)	0.0556 (-0.0355 to 0.1427)	Moderate	N/A	N/A	N/A	N/A

Table A8*Descriptive Characteristics of Case Studies*

Study	GLP-1	Gender	Age
Dardano 2022	Dulaglutide	Female	55
de Lucas 2014	Liraglutide	Male	62
Diamont 2012	Liraglutide	Male	57
Oriot 2011	Exenatide	Male	47
Sheffield 2007	Exenatide	Male	40