The Impact of Novel Antidiabetic Medications Among People with HIV

by

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A Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
of The University of Manitoba
in partial fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

College of Pharmacy

Rady Faculty of Health Sciences

University of Manitoba

Winnipeg

Thesis Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have proven metabolic and kidney benefits in the general population, but evidence among people with HIV (PWH), a population with high comorbidity burden, is limited. This thesis evaluated their safety and effectiveness in PWH, focusing on bodyweight, glycemic control, kidney function, and depressive symptoms.

Methods: Four observational studies were conducted using data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a multicenter cohort of PWH in care across the US (2013–2024). Study 1 assessed one-year changes in bodyweight and hemoglobin A1c (HbA1c) following semaglutide initiation. Study 2 used a new-user, active-comparator design to compare weight outcomes across four antidiabetic classes: GLP-1RAs, SGLT2is, dipeptidyl peptidase-4 inhibitors, and sulfonylureas. Study 3 applied propensity score matching to compare SGLT2is versus other antidiabetic classes on acute estimated glomerular filtration rate (eGFR) decline (≥10% and ≥30% at 6 months) and longer-term eGFR trajectories. Study 4 used a pre-post design to evaluate changes in depressive symptoms (Patient Health Questionnaire-9; PHQ-9) after semaglutide initiation. Continuous outcomes were analyzed using linear mixed models, and time-to-event outcomes using Cox proportional hazards models.

Results: In Study 1, semaglutide initiation was associated with a mean weight reduction of 6.47 kg (95% CI: -7.71, -5.23) and an HbA1c reduction of 1.07% (95% CI -1.64, -0.50). In Study 2, GLP-1RAs were associated with the greatest weight loss (4.44%; 95% CI -5.51, -3.36), particularly among individuals without diabetes, with obesity, and those receiving semaglutide. SGLT2is were

associated with modest weight loss, while other classes showed minimal changes. In Study 3 (295 matched pairs), SGLT2i use was associated with higher rates of acute eGFR decline (≥10%: aHR 1.79 [95% CI 1.40–2.28]; ≥30%: aHR 1.69 [95% CI 1.05–2.73]), although the mean decline was small (-2.6 mL/min/1.73 m²) and appeared transient over time. In Study 4, semaglutide was not associated with worsening depressive symptoms (mean PHQ-9 change: -0.1; 95% CI: -0.7, 0.5).

Conclusion: Among PWH, GLP-1RAs, particularly semaglutide, were associated with clinically meaningful weight and HbA1c reductions without evidence of worsening depressive symptoms, while SGLT2is were associated with modest weight loss and generally favorable kidney outcomes.

Acknowledgements

This work would not have been possible without the guidance, encouragement, and support of many people, to whom I am profoundly grateful.

I would like to express my sincere gratitude to my supervisor, Dr. Sherif Eltonsy, for your exceptional mentorship, patience, and guidance throughout this PhD journey. Your thoughtful advice and encouragement, especially during the more difficult periods, have shaped both this research and my growth as a scientist. Thank you for always believing in me.

I am also deeply grateful to my co-supervisor, Dr. Chris Delaney, for your patience, support, and insightful guidance. Your mentorship, especially through complex statistical and methodological challenges, has been invaluable and has strengthened both this research and my confidence as a researcher. I am especially grateful for the statistics and epidemiology lessons, which I will always carry forward throughout my career.

I also thank my committee members, Dr. Malcolm Doupe and Dr. Christine Leong, for your valuable feedback, critical insights, and support.

I am also thankful to the CNICS research team at the University of Washington—Heidi, Stephanie, Robin, Bridget, Lydia, and many others—for your collaboration and support. The weekly CNICS meetings were a highlight of my week and provided many opportunities to learn from all of you, including the memorable whiteboard discussions with Dr. Delaney.

To my first friends and colleagues in the lab, Alekhya and Laila, thank you for making Winnipeg feel like home when I first arrived, and for helping me navigate the PhD journey. I am grateful for

your friendship, support, and for sharing so many memorable moments, including our conference trips, laughs, and meaningful conversations. Alekhya, I also want to thank you for being a safe space where I could always share my thoughts without judgement. I would also like to thank Sam, Faiza, and Naira for their support and for making the lab an enjoyable place. To my friend and colleague, Mira, having you here has made this journey feel like a home away from home. I am grateful for all the fun and deep conversations we've shared. To the rest of the Pharmacy graduate students, thank you. Pharmacy grad events were always fun to be a part of, and it was a pleasure getting to know you all.

I gratefully acknowledge the financial support provided by the University of Manitoba Graduate Fellowship, William G. Eamer Graduate Achievement Fellowship, and the Manitoba Training Program (MTP) for Health Services Research. I am particularly grateful to the MTP program and Dr. Doupe for encouraging me to consider the broader impact of my work, think beyond the immediate research question, and always ask, "so what."

Finally, to my mother, Lama. Your selfless support during my serious illness and throughout this challenging journey made this work possible. Because of you, I was able to continue, to finish, and to grow. To my sister, Gheeda, thank you for always being there, cheering me on through both the challenges and triumphs of this journey. To the rest of my family and friends, thank you for listening, supporting, and walking this journey with me. Your belief in me and steady presence have meant more than I can say.

Dedication

To my mother, you didn't just support me—you made this journey possible. You gave me life, not once but twice, and your love, courage, and sacrifice have shaped everything I am. Even in moments when I doubted myself, your belief in me never stopped and gave me the strength to keep going.

To my father, though you are no longer here, your belief in me and the values you instilled continue to guide me every day. I hope I have made you proud.

To all people living with HIV, you have come so far, faced so much, and still push on. Your resilience and strength inspire all of us and remind us to keep fighting stigma and pushing forward.

This thesis is dedicated to you, with all my love and gratitude.

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List of Abbreviations

aHR	Adjusted Hazard Ratio
ASCVD	Atherosclerotic Cardiovascular Disease
ART	Antiretroviral Therapy
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNICS	Centers for AIDS Research Network of Integrated Clinical Systems
CVD	Cardiovascular Disease
DPP-4i	Dipeptidyl Peptidase-4 Inhibitor
eGFR	Estimated Glomerular Filtration Rate
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA1c	Hemoglobin A1c
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
ITT	Intention-to-treat
LMM	Linear Mixed Model
MACE	Major Adverse Cardiovascular Events
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PHQ-9	Patient Health Questionnaire-9
PI	Protease Inhibitor
PS	Propensity Score
PWH	People With HIV
RCT	Randomized Controlled Trial
ROR	Reporting Odds Ratio
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
SU	Sulfonylurea
T2D	Type 2 Diabetes

TAF	Tenofovir Alafenamide
TDF	Tenofovir Disoproxil Fumarate
VL	Viral Load

Preface

This thesis is presented in a manuscript-based format. Chapters 2 through 5 consist of original research manuscripts that have been published or prepared for publication in peer-reviewed journals. Each manuscript chapter is preceded by an overview that connects it to the overarching objectives of the thesis and situates it within the broader research objectives. Chapters which have been published or accepted for publication also include the citation. All studies were conceptualized and executed by Lara Haidar, with contributions from her thesis advisors and advisory committee: Dr. Sherif Eltonsy (primary advisor), Dr. Joseph A.C. Delaney (co-advisor), Dr. Christine Leong (committee member), and Dr. Malcolm B. Doupe (committee member). Lara Haidar is fully responsible for the integrity of the manuscripts, accuracy of analysis and interpretation. All co-authors contributed to interpreting the findings, reviewing the results, and revising the manuscript. Manuscripts have been revised according to feedback from all authors, and final approval from co-authors was obtained prior to publication.

This thesis consists of six chapters: an introductory chapter, four manuscript chapters (Chapters 2–5), and a concluding chapter. The manuscripts included in this thesis are:

1. Weight Loss Associated with Semaglutide Treatment Among People with HIV
2. Comparative Effectiveness of GLP-1 Receptor Agonists, SGLT2 Inhibitors, DPP-4 Inhibitors, and Sulfonylureas on Weight Change in People with HIV: A Real-World Longitudinal Cohort Study
3. Impact of SGLT2 Inhibitors on Kidney Function Among People with HIV: A US Prospective Multi-Site Study
4. Safety of Semaglutide on Depressive Symptoms Among People with HIV in Routine Clinical Care

Chapter 1. Introduction, Literature Review, and Thesis Objectives

1.1 Background, Rationale, and Overview of Objectives

With the advent of the highly active antiretroviral therapy (ART), people with HIV (PWH) now have a prolonged life expectancy and a better quality of life.[1,2] Despite these advances, PWH in the modern HIV era experience a high prevalence of complications typically associated with aging, including cardiovascular disease,[3] chronic kidney disease (CKD),[4] metabolic syndrome and obesity,[5] type 2 diabetes (T2D),[6] metabolic-associated steatotic liver disease (MASLD) formerly known as non-alcoholic fatty liver disease (NAFLD),[7,8] and mental health disorders such as depression.[9]

The epidemiology of these comorbidities has shifted markedly in the modern ART era.[10] Globally, about half of PWH are now aged 50 years or older, and the prevalence of non-communicable diseases is higher than in HIV-negative populations.[10] Cardiovascular disease risk is 1.5–2 times higher,[11,12] metabolic syndrome affects 20–27%,[13,14] and diabetes occurs in 10–15%, roughly twice the rate of HIV-negative individuals.[6,15–27] MASLD affects around 40%,[7] CKD (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²) 5–10% (2–5 times higher),[28] and depression 20–40% (about three times higher).[29,30] Many of these conditions occur at younger ages and progress more rapidly than in the general population.[31,32] By 2030, an estimated 45% of PWH on ART will have at least two physical comorbidities and 64% at least one mental health condition.[33] Overall, PWH spend 10–15 additional years living with one or more major comorbidities compared to HIV-negative individuals.[34] These comorbidities arise from the combined effects of HIV-related chronic inflammation, immune dysregulation, antiretroviral therapy, and lifestyle factors.[35] In addition, many PWH face social challenges, including stigma,

economic marginalization, mental health disorders, and substance use, which further increase their risk of chronic disease and complicate its management.[36,37] Taken together, these intersecting clinical, behavioral, and social factors make PWH a unique population with distinct health needs and responses to treatment.

Managing HIV in the modern era therefore requires not only viral suppression but also strategies to address these comorbidities. Addressing both HIV and multiple complex comorbidities is challenging and requires evidence-based treatment strategies. In recent years, the therapeutic landscape for T2D has undergone a paradigm shift with the introduction of novel antidiabetic medications, including glucagon-like peptide-1 receptor agonists (GLP-1RA), dual GLP-1/gastric inhibitory polypeptide (GIP) receptor agonists, and sodium-glucose co-transporter 2 inhibitors (SGLT2i). These agents lower blood glucose and hemoglobin A1c (HbA1c) while providing additional benefits beyond glycemic control.[38] Currently, there are no specific guidelines for managing diabetes among PWH, and current treatment is largely based on recommendations from the general population.

In the general population, current American Diabetes Association (ADA) guidelines and Diabetes Canada guidelines for type 2 diabetes emphasize a comorbidity-driven approach, prioritizing agents with proven cardiovascular and renal benefits, such as the GLP-1RAs and SGLT2 inhibitors.[39,40] Metformin is still used as the initial agent for most individuals due to its efficacy, safety profile, and affordability, and commonly serves as a foundation for combination therapy. For patients with atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk, either GLP-1RA or SGLT2i with proven cardiovascular benefit is recommended.[39,40] People with chronic kidney disease generally receive SGLT2i, although GLP-1RA with renal benefit, such as

semaglutide, may also be considered.[39–41] For patients with heart failure, SGLT2i are preferred. For weight management, newer GLP-1RAs such as semaglutide and tirzepatide are generally recommended.[39,40] Other GLP-1RAs, such as liraglutide, provide modest weight loss, and SGLT2i can also decrease weight but to a lesser degree.[42,43] These recommendations are supported by multiple randomized controlled trials showing that GLP-1RA and SGLT2 inhibitors reduce major adverse cardiovascular events (MACE), cardiovascular mortality, and kidney disease progression.[44–46] Other commonly used second-line antidiabetic agents, including sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors, generally lack the broader cardiovascular, renal, and weight-related benefits seen with GLP-1RA and SGLT2i.[47]

GLP-1RA and SGLT2 inhibitors have been shown to have other health-related benefits. Current research also explores their potential impacts on MASLD and metabolic dysfunction-associated steatohepatitis (MASH). In August 2025, the FDA approved injectable high-dose semaglutide for treating adults with MASH and moderate to advanced liver fibrosis.[48–50] Beyond these established effects, studies are investigating the effects of GLP-1RA on cognitive function, including Alzheimer's disease and Parkinson's disease,[51] as well as their potential role in treatment of alcohol and substance use disorders.[52–55]

Despite the benefits of GLP-1RAs and SGLT2 inhibitors in the general population, their safety and effectiveness have been insufficiently studied in PWH, who were largely excluded from the pivotal clinical trials. PWH have unique clinical, social, and behavioral factors that may influence disease progression, treatment response, and medication adherence, highlighting the need for population-specific evidence to guide the use of novel antidiabetic therapies in this population ensuring optimal, safe, and equitable care.

Building on these knowledge gaps, this **thesis aims to evaluate the safety and effectiveness of novel antidiabetic medications among PWH.** The first objective is to assess the impact of GLP-1RAs, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas on body weight and glycemic control. The second objective examines the safety and preliminary effectiveness of SGLT2 inhibitors on kidney function, considering both short-term changes in eGFR and longer-term eGFR trajectories. The third objective assesses the safety of semaglutide with respect to depressive symptoms, acknowledging emerging concerns about potential mood-related adverse effects.

The remaining sections of Chapter 1 will expand on the relevant literature regarding metabolic, renal, and mental health comorbidities in PWH, as well as the evidence for novel antidiabetic therapies, and will conclude with the rationale and specific objectives of this thesis.

1.2 Metabolic, Renal, and Mental Health Comorbidities in People with HIV

This section reviews the epidemiology, mechanisms, and risk factors underlying obesity, kidney, and mental health comorbidities among PWH, highlighting how HIV-specific factors and antiretroviral therapy contribute to these conditions.

1.2.1 Obesity and weight gain

1.2.1.1 Epidemiology of Obesity in People with HIV

Advancements in and early initiation of ART have significantly reduced HIV-associated wasting among PWH. However, in contrast, there has been a notable increase in weight gain and obesity, mirroring the obesity epidemic observed in the general population.[5,56–61]

In high-income countries, several cohort studies have documented a rising burden of obesity in PWH. In the NA-ACCORD cohort (United States and Canada), the proportion of PWH with obesity at ART initiation nearly doubled from 9% in 1998 to 18% in 2010, and over 20% of those with normal BMI progressed to overweight or obesity within three years.[62] The U.S. Veterans Aging Cohort Study reported that although PWH had lower baseline rates of obesity compared to HIV-negative controls, they experienced greater weight gain after starting ART, especially during the first one to two years.[63] Similarly, in the French COPANA cohort, 20% of PWH with normal BMI at ART initiation became overweight or obese after 36 months, with higher weight gain among people of sub-Saharan African origin.[64]

Similar patterns of weight gain have emerged in low- and middle-income settings. A study of around 8,000 ART-experienced adults in Uganda found that 28% were overweight and 18% were obese, with higher prevalence among women and those with longer ART duration.[65] In China, the prevalence of obesity among ART-naïve PWH more than doubled between 2014 and 2020.[66] In

Ethiopia, a prospective cohort found that 31% of individuals starting an ART regimen of tenofovir/lamivudine/dolutegravir experienced excessive weight gain. Females, middle-aged individuals, and those with detectable viral load were more likely to experience this weight gain.[67] These findings demonstrate that obesity is a growing concern in high, middle, and lower-income countries.

1.2.1.2 Pathophysiological Mechanisms of Weight Gain

Weight gain in PWH is multifactorial. Lifestyle and demographic factors, such as aging, diet, and reduced physical activity, contribute to this trajectory.[5] In addition, chronic inflammation and persistent immune activation remain present in many PWH despite effective viral suppression with ART.[68] This ongoing inflammatory state disrupts normal metabolic regulation, promotes adipose tissue dysfunction, and contributes to insulin resistance, each of which can facilitate fat accumulation and weight gain.[69] Immune cells within adipose tissue, particularly macrophages and T cells, release pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, and chemokines like MCP-1, which impair insulin signaling and adipocyte function.[70–76] Persistent HIV reservoirs in adipose tissue further sustain local and systemic inflammation, promoting ectopic fat deposition in organs such as the liver and skeletal muscle and worsening insulin resistance. [70–76] Over time, this impaired fat metabolism and chronic inflammatory signaling favor the accumulation of visceral and subcutaneous fat, contributing to overall obesity and increasing the risk of metabolic complications in PWH.

1.2.1.3 Patterns and Determinants of ART-Associated Weight Gain

ART plays a central role in the increase in obesity. In the early ART era, weight gain after treatment initiation often reflected a “return to health” phenomenon, as viral suppression and immune

recovery allowed individuals to regain weight lost during untreated HIV infection and HIV-associated wasting.[77] In the modern ART era, weight gain often occurs beyond this recovery effect and may be driven by the direct pharmacologic effects of certain ART agents.[77]

Weight gain after ART initiation is common. While most PWH gain less than 5% of their body weight, some, particularly women and Black individuals, experience increases of more than 10%.[69,78,79] Most weight gain occurs within 12 months of starting ART, and is most pronounced in those with advanced HIV (low CD4 count), where mean weight gain can exceed 8–10 kg over two years, compared to 2–3 kg in those with early HIV presentation.[80,81] One long-term study following PWH for nearly 10 years observed an average weight increase of 3.6 kg during the first 48 weeks after ART initiation and a total of 7.1 kg over the full 480 weeks of follow-up.[82] By the end of the study period, 40% of participants had gained more than 10% of their baseline weight. It is also important to note that the pattern of weight gain in PWH can vary. Some PWH develop lipohypertrophy, characterized by preferential accumulation of visceral or abdominal fat.[83,84] This pattern of weight gain may carry additional cardiometabolic risk.[84]

Specific ART agents are associated with greater weight gain than others. Integrase strand transfer inhibitors (INSTIs) (e.g., dolutegravir and bictegravir) and the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir alafenamide (TAF) are consistently associated with greater weight gain compared to older regimens.[85,86] These drugs are now commonly included in first-line ART regimens, which may partly explain recent increases in average BMI among PWH initiating treatment.[87] In a pooled analysis of randomized controlled trials, weight gain over 96 weeks was highest among INSTI users, who gained an average of 3.24 kg (95% CI, 3.02–3.46). Among INSTI agents, the greatest increases were seen with bictegravir (4.24 kg, 95% CI, 3.71–4.78) and

dolutegravir (4.07 kg, 95% CI, 3.51–4.62), while elvitegravir/cobicistat was associated with smaller gains (2.72 kg, 95% CI, 2.45–3.0). In contrast, NNRTI and PI users gained less weight, averaging 1.93 kg (95% CI, 1.58–2.28) and 1.72 kg (95% CI, 1.01–2.42), respectively.[88] Individuals with ≥10% weight gain were more likely to be female or black, have a lower baseline weight or BMI, have lower baseline CD4 cell count, and have higher HIV viral load.[88] In the ADVANCE trial over 96 weeks, mean weight gain was substantial (7.1 kg [SD 7.4] in the tenofovir alafenamide, emtricitabine, and dolutegravir group; 4.3 kg [6.7] in the tenofovir disoproxil fumarate, emtricitabine, and dolutegravir group, and 2.3 kg [7.0] in the tenofovir disoproxil fumarate, emtricitabine, and efavirenz group), and was greater among women than men.[89] In rural Tanzania, the KIULARCO cohort showed that obesity incidence after 18 months was significantly higher with dolutegravir-based ART (10.9%) compared to efavirenz-based ART (5.1%).[90]

Older ART regimens, particularly early NRTIs and protease inhibitors (PIs), were associated with adverse changes in adipose distribution.[21,56,84,88,91,92] These agents lead to increased central adiposity and reduced peripheral fat, even in the absence of overt lipodystrophy or significant changes in total body fat. In addition to altering fat distribution, these regimens contribute to the dysregulation of glucose and lipid metabolism thus increasing the risk of insulin resistance, dyslipidemia, and metabolic syndrome.[20,91,93,94] These early concerns have shifted in the modern ART era, where generalized weight gain, rather than fat redistribution, has emerged as the dominant issue.

1.2.1.4 Management and Clinical Implications

The Infectious Diseases Society of America recommend regular monitoring of weight and BMI, counseling on lifestyle modification, and annual screening for diabetes and cardiovascular risk in

people on INSTI- or TAF-based regimens.[87,95] Lifestyle interventions (diet & exercise) are first-line treatments to manage excessive weight gain; pharmacologic options such as GLP-1 agents (e.g., semaglutide) may be considered, but data in HIV populations are limited.[95] Switching ART regimens to mitigate weight gain is generally ineffective and not recommended.[87,95]

The clinical implications of obesity in PWH are significant. Obesity is strongly associated with insulin resistance, a precursor to type 2 diabetes. PWH already face a higher baseline risk of T2D due to chronic inflammation, immune dysregulation, and ART-related metabolic side effects.[15,70,83,96] Excess adiposity, especially visceral fat, exacerbates these risks.[15,70,83,96] In addition, obesity is an established risk factor for cardiovascular disease, another leading cause of morbidity and mortality in this population.[12] Studies have shown that obesity contributes to elevated blood pressure and dyslipidemia among PWH, compounding traditional and HIV-specific cardiovascular risk factors.[97,98]

In conclusion, obesity among PWH represents a growing challenge in HIV care that requires targeted clinical attention and ongoing research.

1.2.2 Kidney Disease

1.2.2.1 Epidemiology of Kidney Disease in HIV

As ART has markedly improved life expectancy, non–AIDS-related comorbidities such as kidney disease have become leading health concerns among PWH. Kidney disease now represents a major cause of morbidity and mortality.[99,100] Both chronic kidney disease (CKD) and acute kidney injury (AKI) occur more frequently in PWH than in the general population, reflecting a complex interplay of traditional, metabolic, ART-related, and HIV-specific factors.[4,101–103]

Prevalence estimates for CKD vary widely depending on population characteristics and the equation used to estimate kidney function. A systematic review and meta-analysis of 209,078 adults with HIV across 60 countries found a global CKD prevalence of 6.4% when using the Modification of Diet in Renal Disease [MDRD] equation, 4.8% when using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation, and 12.3% using the Cockcroft-Gault equation, with the highest rates in Africa.[104] The AGEhIV Cohort Study found that HIV infection was independently associated with renal impairment (eGFR <60 mL/min/1.73m^2; adjusted odds ratio 2.1), as well as albuminuria (aOR 5.8) and proximal tubular dysfunction (aOR 7.0) compared to people without HIV.[105] Another meta-analysis reported that the risk of renal disease was 3.87 folder higher (95% CI 2.85–6.85) among PWH compared to those without HIV.[106]

AKI is also common in PWH particularly among hospitalized individuals. In a large cohort of 173,884 hospitalized patients, including 4,718 with HIV, both virally suppressed and unsuppressed individuals had an increased risk of AKI compared with those without HIV (adjusted hazard ratios [aHR] 1.27 and 1.73, respectively) and a higher risk of AKI requiring kidney

replacement therapy (aHR 1.89 and 1.87, respectively).[107] These findings indicate that, regardless of virologic control, HIV remains an independent risk factor for AKI among hospitalized patients.

1.2.2.2 Pathophysiology and Risk Factors

The pathophysiology of kidney disease in HIV is multifactorial, encompassing direct viral effects, immune dysregulation, ART-induced nephrotoxicity, and traditional comorbidities.

HIV-Related Factors

HIV can directly infect renal epithelial cells leading to HIV-associated nephropathy (HIVAN), a collapsing form of focal segmental glomerulosclerosis characterized by podocyte proliferation and microcystic tubular dilation.[108–110] HIVAN was first described in 1983 as a complication of AIDS. [111] HIVAN primarily affects individuals of African ancestry due to APOL1 high-risk alleles, predisposing people to kidney injury.[112] Although the widespread use of ART has substantially reduced the incidence of HIVAN, chronic inflammation, immune activation, and residual viral replication can persist even in virally suppressed individuals, accelerating CKD progression. [113,114]

Coinfection with hepatitis B (HBV) or hepatitis C (HCV), which are highly prevalent in PWH, further elevates the risk of CKD. HCV coinfection, in particular, confers a 60–100% higher CKD risk compared with HIV alone and is associated with accelerated renal function decline.[115–121]

ART-Related Factors

The introduction of ART has markedly slowed the progression of kidney disease in PWH. In a prospective cohort study of 3,329 patients, before treatment with ART, kidney function was declining by 2.2 mL/min per year. After treatment with ART, the decline slowed to 1.4 mL/min per year, representing a 0.8 mL/min per year improvement in kidney preservation, or roughly 36%.[122]

However, despite these benefits, ART has also introduced new nephrotoxic risks. Among antiretroviral drugs, tenofovir disoproxil fumarate (TDF) and some ritonavir-boosted protease inhibitors (PIs) are most strongly linked to renal toxicity.[110] TDF accumulates in proximal tubular cells, where it disrupts mitochondrial function via intracellular accumulation and depletion of mitochondrial DNA, leading to acute tubular necrosis, and CKD.[123–130] Risk factors for TDF nephrotoxicity include pre-existing renal disease, older age, low body weight, and concomitant use of other nephrotoxic agents.[127] The nephrotoxic potential of TDF is heightened when co-administered with ritonavir-boosted PIs, which increase systemic tenofovir exposure.[122] Most cases are mild and reversible upon drug discontinuation, but severe and irreversible injury can occur.[127] In contrast, tenofovir alafenamide (TAF) is a newer tenofovir prodrug that delivers lower plasma tenofovir exposure than TDF and is therefore associated with substantially reduced nephrotoxicity.[131]

The older, less widely used protease inhibitors, atazanavir and indinavir, may cause crystal-induced nephropathy or obstructive uropathy.[132,133] Other ARTs may cause indirect effects on creatinine levels without true renal injury. For instance, dolutegravir, cobicistat, and rilpivirine inhibit tubular creatinine secretion, leading to modest serum creatinine increases that may falsely suggest eGFR decline.[134]

Traditional Risk Factors

As PWH live longer, traditional CKD risk factors such as hypertension, diabetes, obesity, and cardiovascular disease have become increasingly important contributors to kidney disease.[4,103] These metabolic comorbidities often coexist with an aging HIV population, compounding risk.

1.2.2.3 Acute Kidney Injury (AKI) in HIV

AKI is a frequent and serious complication in PWH, characterized by a rapid decline in renal function and associated with increased morbidity and mortality. [102,107,135] Both HIV-dependent factors (e.g., low CD4 count, high viral load, and AIDS-defining illnesses) and HIV-independent factors (e.g., older age, pre-existing chronic kidney disease, diabetes, hypertension, and hepatitis C coinfection), contribute to AKI risk.[136–140] Select medications, particularly antiretrovirals like tenofovir further increase susceptibility.[136] The pathogenesis of AKI in PWH is multifactorial, encompassing pre-renal, vascular, glomerular, tubular, interstitial, and obstructive mechanisms.[136] AKI not only increases short-term mortality but also has long-term consequences, including progression to chronic kidney disease and cardiovascular complications.[135,136] These long-term risks highlight the need for early identification of at-risk patients, careful monitoring of renal function, and strategies to prevent nephrotoxicity.[110]

1.2.2.4 Detection and Management

Kidney disease in PWH is often asymptomatic until advanced stages, highlighting the importance of routine screening. CKD is diagnosed based on persistent eGFR <60 mL/min/1.73 m² or evidence of kidney damage (e.g., proteinuria) for at least three months.[28]

Estimation of glomerular filtration rate (eGFR) in PWH is challenging and often underestimates true kidney function.[141] Commonly used equations include the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft–Gault formulas.[110] Among these, the CKD-EPI equation generally provides the most accurate estimates in adults with HIV, particularly in those with stable viral suppression.[142–144] The Cockcroft–Gault remains preferred for ART dose adjustments.[110] The original CKD-EPI creatinine

equation included race (Black or non-Black) as a variable, along with age, sex, and serum creatinine, to estimate eGFR.[145] In 2021, the National Kidney Foundation–American Society of Nephrology (NKF–ASN) recommended a race-free version.[146] The race-free CKD-EPI equation has been evaluated in a large observational cohort study of around 69,000 PWH. Use of the race-free equation reclassified approximately 16% of Black participants to lower eGFR categories, improving risk prediction and detection of CKD progression.[147] These participants also had a higher prevalence of CKD risk factors and a higher risk of progression across all GFR stages compared to White participants,[147] highlighting the clinical utility of the race-free equation for identifying Black PWH at increased risk of CKD and supporting its use as the preferred equation in this population. However, in studies from Malawi, Uganda, and South Africa, creatinine-based equations, including the race-free CKD-EPI formula, substantially underestimated kidney disease prevalence compared with measured GFR, whereas cystatin C–based equations provided more accurate estimates across all GFR levels. [148] However, cystatin C testing remains limited in availability, and its concentrations can be influenced by systemic inflammation and HIV viremia, potentially confounding interpretation in people with HIV.[143,149]

It is important to note that all eGFR formulas tend to underestimate true GFR in PWH due to several HIV-specific factors. Sarcopenia and low muscle mass, common consequences of chronic HIV infection and inflammation, reduce creatinine production, leading to overestimation of kidney function.[150–153] Furthermore, certain ART such as dolutegravir, bictegravir, cobicistat, and rilpivirine inhibit tubular creatinine secretion, causing artificial elevations in serum creatinine (typically 0.1–0.2 mg/dL) that do not indicate true renal injury.[134] This results in an artificial reduction in creatinine-based estimated GFR (eGFR), which can be misinterpreted as renal

impairment if clinicians are unaware of the drug effect. In such cases, cystatin C–based estimates, particularly the combined CKD-EPI creatinine–cystatin C equation, may be used to improve accuracy and distinguish between drug-related creatinine changes and genuine kidney dysfunction.[149,154–157] Cystatin C is freely filtered at the glomerulus and not secreted or reabsorbed by renal tubules.[158]

Management of CKD in people living with HIV combines general kidney-protective strategies with HIV-specific considerations.[28] For those not yet on ART, therapy should be initiated promptly. In patients already receiving ART, regimens containing nephrotoxic agents such as TDF should be switched to safer alternatives (e.g., TAF) when possible. Nucleoside reverse transcriptase inhibitors (NRTIs) and other renally excreted medications may require dose adjustments based on kidney function.[159] Beyond ART optimization, management largely mirrors that of the general population: controlling blood pressure and diabetes, addressing reversible risk factors (e.g., hyperglycemia, hyperuricemia, hyperlipidemia, hypertension, lifestyle factors, and co-infections), and implementing lifestyle interventions such as diet, exercise, and smoking cessation.[95,160] Regular monitoring of eGFR and proteinuria/albuminuria is essential to detect disease progression early, and referral to nephrology should be considered for advanced CKD (eGFR < 30 mL/min/1.73 m²) or rapid decline.[95,160] Renin–angiotensin system blockade (angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) may help reduce proteinuria and slow progression in those with albuminuria or proteinuria.[95,160,161]

1.2.3 Depression

1.2.3.1 Epidemiology of Depression in HIV

Depression is one of the most common psychiatric comorbidities of PWH, with an estimated prevalence of 20% to 40%,[162] a rate 2 – 4 times higher than in the general population.[163–166] Depression is associated with adverse outcomes across the HIV-care continuum, including lower antiretroviral therapy (ART) adherence, reduced viral suppression, and increased morbidity and mortality.[167,168]

Recent studies highlight the high burden of depression across diverse populations of PWH. In a 2024 study using data from the United States All of Us Research Program including over 412,000 individuals, 43% of the 5,193 participants living with HIV were diagnosed with major depression, nearly double the 22% prevalence observed among those without HIV.[169] A systematic review of 118 studies encompassing over 51,000 individuals, reported a pooled prevalence of depression among people with HIV/AIDS of 31% (95% CI: 28%–34%).[162] Regional variation was evident, with the highest prevalence in South America (44%; 95% CI: 35%–53%) and the lowest in Europe (22%; 95% CI: 17%–27%).[162] For comparison, the World Health Organization estimates the global prevalence of depression in the general population at approximately 3.8%, including 5% among adults, and 5.7% among adults over 60 years of age.[170] Rates of depression may be even higher among women, racialized individuals, and sexual and gender minorities living with HIV, reflecting intersecting social and structural vulnerabilities.[171,172]

While the introduction of effective ART has improved life expectancy, it has not reduced the burden of mental health conditions, which remain underdiagnosed and undertreated in this

population. Despite efforts to screen for depression, underdiagnosis remains common; one study found that depressive syndromes were undiagnosed in 26% of PWH.[30]

1.2.3.2 Mechanisms Underlying Depression in People with HIV

Several interrelated mechanisms have been proposed to explain the increased risk of depression among PWH, spanning biological, psychological, and social domains.[165,173–176] Chronic immune activation and low-grade systemic inflammation persist even in individuals with well-controlled HIV, likely due to residual viral replication, microbial translocation, and immune system dysregulation.[165,173–176] This ongoing inflammatory state may contribute to neuroinflammation, which has been implicated in the pathophysiology of depression through effects on neurotransmitter systems, particularly serotonin, dopamine, and glutamate.[165,173–176] HIV may also directly impact the central nervous system by infecting resident immune cells such as microglia and macrophages, leading to structural and functional changes in brain regions involved in emotion regulation, including the prefrontal cortex, hippocampus, and amygdala.[165,173–176] Neuroendocrine dysregulation, particularly chronic hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, further contributes to depression in PWH by causing persistently elevated cortisol levels and altered neuroactive steroid balance, which promote neuroinflammation and impair neurotransmission in mood-regulating brain regions.[177–180] Some ART regimens, especially those containing efavirenz or INSTIs such as dolutegravir, have been associated with neuropsychiatric adverse effects, including sleep disturbances, anxiety, and depressive symptoms.[181]

Psychologically, living with chronic illnesses such as HIV can lead to ongoing stress and internalized stigma.[181,182] Many individuals experience periods of anticipatory anxiety regarding health

outcomes, disclosure of HIV status, and potential social rejection.[181,182] One study showed that approximately 80% of PWH report experiencing some type of stigma related to HIV/AIDS status.[183]

Social and structural factors play a major role in shaping depression risk among PWH. Housing instability, unemployment, food insecurity, discrimination, and a history of trauma or abuse are more prevalent in this population and have been independently associated with depression.[181,184] Moreover, PWH are more likely to use substances which also contributes to higher rates of depression.[185] These social and structural disadvantages are not only stressors themselves but also barriers to accessing timely and effective mental health care. Importantly, these biological, psychological, and social mechanisms do not act in isolation. These factors interact with one another, where biological, psychological, and social drivers converge to heighten the risk of depression.

1.2.3.3 Clinical Consequences of Depression

Depression in PWH is associated with a wide range of adverse outcomes including lower viral load suppression rates, poorer ART adherence, and increased risk of HIV-related morbidity and mortality.[168,186] A meta-analysis of 16 studies involving over 80,000 participants found that individuals without depression were 30% more likely to achieve viral suppression compared to those with depression (OR 1.30; 95% CI: 1.15–1.48).[187] Moreover, in a U.S. cohort study of approximately 6,000 adults with HIV, each 25% increase in time spent with depression was associated with an 8% higher risk of missed clinic appointments, a 5% higher risk of having a detectable viral load, and a 19% increased risk of death.[167]

In addition to its effects on HIV outcomes, depressive symptoms also contribute to lower quality of life and heightened risk of substance use disorders.[188] Also, depression has been identified as

an independent risk factor for cardiovascular disease,[189,190] which is already elevated in this population due to traditional risk factors and HIV-related factors.[191] Despite its impact, depression remains underrecognized[30] and inadequately managed[192,193] in many HIV care settings, highlighting the need for integrated approaches that address both mental and physical health.

1.2.3.4 Screening and Diagnosis

Depression in PWH typically manifests as persistent sadness, anhedonia, fatigue, sleep disturbances, changes in appetite, and cognitive difficulties, and often co-occurs with anxiety, post-traumatic stress disorder (PTSD), substance use, and other neurocognitive impairments.[187,194] Recognition can be complicated by symptom overlap with HIV infection or side effects of ART.

Screening for depression in this population is commonly conducted using self-report questionnaires, including the Patient Health Questionnaire-2 (PHQ-2), Patient Health Questionnaire-9 (PHQ-9), Center for Epidemiologic Studies Depression Scale (CES-D), Beck Depression Inventory-II (BDI-II), Hospital Anxiety and Depression Scale (HADS), and the 10-item Kessler Psychological Distress Scale (K10).[195–198] The Infectious Diseases Society of America recommends annual screening for depression in this population, using PHQ-2 and PHQ-9 as the preferred instruments. [95] The PHQ-2 provides a brief initial screen for depressive symptoms while PHQ-9 assesses symptom severity and guides further evaluation. Both instruments have been validated in HIV populations and can be self-administered and completed during clinical encounters.[197,199] For a formal diagnosis, clinician-administered interviews guided by the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria are used, typically through structured tools such as the Structured Clinical Interview for DSM Disorders (SCID), Mini

International Neuropsychiatric Interview (MINI), or Composite International Diagnostic Interview (CIDI), administered by clinicians or trained mental health professionals.[200] Combining self-report screening with clinician confirmation improves diagnostic accuracy, which is particularly important in PWH due to symptom overlap with HIV infection and antiretroviral therapy side effects.

1.2.3.5 Management and Treatment Considerations

Management of major depression in PWH is similar to that in the general population and includes pharmacotherapy, psychotherapy, and, in select cases, electroconvulsive therapy.[201] Prompt recognition and treatment of depression is essential to optimize overall HIV care. Pharmacological options mirror those used in the general population, with selective serotonin reuptake inhibitors (SSRIs) generally considered first-line due to their efficacy and tolerability.[201] Other options include serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.[201] Common SSRIs include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, while SNRIs include venlafaxine, desvenlafaxine, and duloxetine.[201] TCAs remain effective but are limited by anticholinergic side effects and potential cardiotoxicity.[201] Overall, PWH respond to antidepressants similarly to other patients, and no particular agent is superior in this population.[202]

When selecting antidepressant therapy in PWH, careful attention must be paid to potential drug–drug interactions with ART. Many antidepressants are metabolized through cytochrome P450 (CYP) pathways, which can be affected by protease inhibitors or non-nucleoside reverse transcriptase inhibitors.[201] For example, ritonavir, a potent CYP3A4 inhibitor, can increase serum concentrations of TCAs and trazodone, raising the risk of side effects. SSRIs generally have fewer

interactions, but agents such as fluoxetine and paroxetine (CYP2D6 inhibitors)[201] and certain SNRIs, such as venlafaxine (CYP2D6 substrate) and duloxetine (CYP1A2 and CYP2D6 substrate), may also affect CYP enzymes and alter antiretroviral metabolism.

1.3 Novel Antidiabetic Medications: Overview and Mechanisms of Actions

1.3.1 GLP-1 Receptor Agonists

GLP-1RA are a class of medications used to treat T2D and some agents in this class are used to treat obesity.[203] Medications belonging to this class include: semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, and albiglutide (withdrawn from the market in 2018). High dose semaglutide and liraglutide are approved for the treatment of obesity (BMI≥30 kg/m^2) or for overweight (BMI≥27 kg/m^2) patients with comorbidities (e.g. hypertension, T2D, or dyslipidemia).[203] Also, liraglutide, semaglutide, and dulaglutide are indicated for cardiovascular (CV) risk reduction in T2D.[39,40] A full list of medications with their indications is found in Table 1.1.

GLP-1RA exert their pharmacological effects by binding and activating the GLP-1 receptor, thus mimicking the endogenous GLP-1.[204,205] GLP-1 is an incretin hormone secreted by enteroendocrine L-cells in the intestine in response to food intake.[206] It is also secreted by alpha cells in the pancreas and the central nervous system.[207] In patients with T2D the GLP-1 secretion and response is blunted.[206] GLP-1 receptors are widely distributed in the gastrointestinal tract, pancreatic cells, and the central nervous system.[206] When GLP-1RA bind to these receptors, they activate a series of physiological responses. By binding to and activating the GLP-1 receptors in the pancreatic beta cells, insulin is secreted in a glucose dependent manner, which helps lower blood glucose levels by promoting glucose uptake into cells.[206] GLP-1RA also inhibit glucagon secretion from pancreatic alpha cells, which decreases the release of glucose from the liver into the bloodstream.[206] The increase in insulin secretion and synthesis along with the suppression of glucagon release decrease blood glucose levels in a glucose dependent manner.[206] GLP-1RA also delay gastric emptying thus reducing the rate of glucose absorption in the gastrointestinal tract

and decreasing the postprandial glucose spikes, thereby lowering the risk of hypoglycemia. Their weight loss effect is due to GLP-1RA acting centrally by binding to the receptor in the hypothalamus, which thereby increases satiety and reduces appetite.[204–206]

In addition to these established metabolic effects, growing evidence suggests that GLP-1RA may also affect brain function and mood, although the underlying mechanisms remain incompletely understood. GLP-1 receptors are expressed in several brain regions involved in mood regulation, including the prefrontal cortex, hypothalamus, and brainstem. [208] Preclinical studies indicate that GLP-1RA can cross the blood–brain barrier and activate central GLP-1 receptors.[208] Activation of these receptors may contribute to neuroprotective and anti-inflammatory effects, modulation of the kynurenine pathway, and attenuation of neuroinflammatory signaling, processes increasingly recognized in the pathophysiology of depression.[209–212] GLP-1RA may also modulate serotonin signaling in the amygdala and dorsal raphe nucleus, further implicating a neurochemical basis for their potential mood effects.[213] Additionally, GLP-1RA may indirectly improve mood by reducing systemic inflammation and improving metabolic parameters such as insulin resistance and weight,[214] which are associated with depressive symptoms in individuals with diabetes and obesity.

Overall, the potential antidepressant effects of GLP-1RA are likely mediated by central GLP-1 receptor activation in mood-regulating brain regions, modulation of neuroinflammation, and improvement of metabolic and inflammatory states. However, while these mechanisms are biologically plausible and supported by preclinical data, robust clinical evidence for a direct antidepressant effect in humans remains limited and further investigation is needed.

In addition to their role in mood regulation, GLP-1RA are also being investigated for the treatment of addiction, including alcohol and substance use disorders, as they may influence dopamine-mediated reward pathways.[215] A recent randomized phase 2b clinical trial demonstrated that once-weekly semaglutide reduced alcohol consumption and craving in adults with alcohol use disorder, highlighting a potential therapeutic role in addiction management.[216]

Despite their benefits, several barriers hinder the widespread use of GLP-1RA. Common gastrointestinal (GI) side effects, including nausea, vomiting, and diarrhea, affect tolerability,[42] with over 70% of patients in clinical trials reporting adverse events, most of which were mild.[217–219] Although most patients achieve clinically meaningful weight loss, heterogeneity in response exists, and weight loss often plateaus over time.[220–222] High costs further limit access and affordability, particularly among individuals with lower income, and payer coverage of anti-obesity medications remains variable.[223,224] Off-label use of GLP-1RA for weight management also represents a challenge, and drug shortages may limit continued therapy. [225–227] These factors contribute to high discontinuation rates, which in turn can diminish the real-world effectiveness of GLP-1RA. Observational studies report that 1-year discontinuation ranges from 40% to 80%,[228–233] with factors such as cost, insurance coverage, comorbidities, and absence of T2D contributing to early cessation.[228,230] These barriers may be more pronounced in PWH as they often face multiple, intersecting disadvantages—including socioeconomic marginalization, stigma (both internalized and societal), mistrust of the healthcare system, substance use, 2SLGBTQIA+ identity (especially trans and non-binary individuals), and racialized status—which may further limit access to newer therapies such as GLP-1RAs.[234–237]

In this population, the use of GLP-1RA requires careful consideration of HIV-specific factors. Although GLP-1RA are largely metabolized by endopeptidases and have a low potential for cytochrome P450–mediated drug–drug interactions, clinicians should exercise caution when co-administering these agents with atazanavir or oral rilpivirine, as delayed gastric emptying and reduced gastric acid secretion may impair absorption of these antiretrovirals.[238] Gastrointestinal adverse effects, while not shown to be more frequent in HIV-specific trials,[239] may be compounded in PWH with preexisting ART-related GI intolerance, warranting close monitoring. Additionally, GLP-1RA can reduce lean body mass, including skeletal muscle, which is of particular concern in PWH due to higher baseline risks of sarcopenia, frailty, and functional decline.[240,241] Therefore, individualized risk-benefit assessment, alongside counseling on muscle preservation strategies such as resistance training and regular exercise, is recommended.[95] Standard contraindications, including a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2, as well as pregnancy and breastfeeding, remain applicable.[242] Table 1.2 provides a summary of HIV-specific considerations for commonly used antidiabetic medications, including GLP-1RA.

1.3.2 SGLT2 inhibitors

SGLT2 inhibitors are a class of medications used to treat T2D and reduce the CV risk in people with T2D, treat CKD in people with and without diabetes, and heart failure.[243] SGLT2 inhibitors are also known as gliflozins or flozins.[243] Medications belonging to this class include: canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin.[243] The full list of indications for individual medications are listed in Table 1.1. SGLT2 inhibitors decrease blood glucose levels by inhibiting the SGLT2 protein in the proximal renal tubules.[244] SGLT2 is responsible for the majority (around 90%) of glucose reabsorption by the kidneys. Inhibition of this protein leads to an increase in glucose excretion in urine (glucosuria) and a decrease in blood glucose levels.[244] The osmotic diuresis caused by the increased urinary glucose excretion results in reduced intravascular volume and blood pressure. This is thought to play a role in the mechanism of the cardio-protection and improvement of heart failure outcomes of these medications.[245]

SGLT2 inhibitors exert nephroprotective effects primarily by reducing intraglomerular pressure.[246] They decrease glucose and sodium reabsorption in the proximal tubule, which increases sodium delivery to the macula densa.[247] This triggers tubuloglomerular feedback, leading to afferent arteriole vasoconstriction and reduced glomerular hyperfiltration, a key mechanism underlying long-term kidney protection.[247,248] Acutely, this process results in a transient decline in estimated glomerular filtration rate (eGFR), commonly referred to as the eGFR "dip," which typically occurs within the first 2–4 weeks and ranges from 3–6 mL/min/1.73 m^2.[249–252] This early decrease reflects hemodynamic changes rather than structural kidney injury and is generally not harmful.[253] Clinically, discontinuation of SGLT2 inhibitors is unnecessary unless an unexplained eGFR decline exceeds 30%. Kidney Disease: Improving Global Outcomes

(KDIGO) guidelines currently do not recommend monitoring eGFR solely based on SGLT2 inhibitor initiation. [249,254–257]

Despite their benefits, SGLT2 inhibitors are associated with adverse effects, most notably an increased risk of genitourinary infections, including urinary tract infections (UTIs) and mycotic infections. In PWH, these risks warrant special attention. In a study comparing SGLT2 inhibitors to GLP-1RA in PWH, UTIs occurred at similar rates between groups, but mycotic infections were more frequent among SGLT2 inhibitor users.[258] HIV itself is a recognized risk factor for severe infections such as Fournier's gangrene, and the risk may be higher in individuals with uncontrolled HIV or suboptimal adherence to antiretroviral therapy (ART).[259–261] Drug–drug interactions are another key consideration. For example, co-administration of canagliflozin with inducers of UDP-glucuronosyltransferase (UGT) enzyme, such as ritonavir, can reduce canagliflozin plasma levels, and the dose may need to be increased accordingly.[262] Table 1.2 provides a summary of HIV-specific considerations for commonly used antidiabetic medications, including SGLT2 inhibitors.

Table 1.1. Indications of SGLT2 Inhibitors and GLP-1 Receptor Agonists

Medication	Route of Admin	FDA Approval Year	Approved Indications
SGLT2 inhibitors			
Empagliflozin	Oral	2014	• **T2D:** As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥10 years of age with type 2 diabetes mellitus • **CV risk reduction:** Risk reduction of cardiovascular mortality in adults with type 2 diabetes mellitus and established cardiovascular disease. • **Chronic kidney disease:** To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression. • **Heart failure:** Risk reduction of cardiovascular mortality and hospitalization for heart failure in adults with heart failure.
Dapagliflozin	Oral	2014	• **T2D:** As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥10 years of age with type 2 diabetes mellitus • **CV risk reduction**: Risk reduction of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. • **Chronic kidney disease:** To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with CKD. • **Heart Failure:** Risk reduction of cardiovascular mortality, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure.
Canagliflozin	Oral	2013	• **T2D:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • **CV risk reduction:** To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease • **CKD risk reduction:** To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure *in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria*

Ertugliflozin	Oral	2017	• **T2D:** As an adjunct to diet and exercise to improve glycemic control in adults with T2D
Medication	**Route of Admin**	**FDA Approval Year**	**Approved Indications**
GLP-1 Receptor Agonists/ Dual Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1RA			
Exenatide	SC	2005	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults with T2D.
Liraglutide	SC	2010	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥10 years of age. • **CV Risk Reduction**: Reduces risk of major adverse cardiovascular events in adults with T2D and established CVD. • **Obesity**: Chronic weight management in adults and pediatric patients ≥12 years of age with obesity or overweight with weight-related comorbidities.
Albiglutide	SC	2014 (withdrawn in 2018)	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults with T2D.
Dulaglutide	SC	2014	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥10 years of age. • **CV Risk Reduction**: Reduces risk of major adverse cardiovascular events in adults with T2D and established CVD.
Lixisenatide	SC	2016	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults with T2D.
Semaglutide	SC/Oral	2017	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥10 years of age. • **Obesity**: Chronic weight management in adults with obesity or overweight with weight-related comorbidities (subcutaneous form doses 1.7/2.4 mg). • **CV Risk Reduction**: Reduces risk of major adverse cardiovascular events in adults with T2D and established CV disease. • **CKD in type 2 diabetes:** Reduce risk of sustained eGFR decline, end-stage kidney disease, and CV death in adults with T2D and CKD • **MASH:** treatment of noncirrhotic MASH with moderate to advanced fibrosis (F2–F3) in adults, as an adjunct to diet and exercise

Tirzepatide	SC	2022	• **T2D**: As an adjunct to diet and exercise to improve glycemic control in adults with T2D. • **Obesity**: Chronic weight management in adults with obesity or overweight with weight-related comorbidities. • **Obstructive sleep apnea:** Treat moderate to severe OSA in adults with obesity. (Only 10 or 15 mg injected subcutaneously)

Reference: U.S. Food and Drug Administration. Drugs@FDA database. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Individual prescribing information was consulted for each medication.

Abbreviations: SGLT2 inhibitors: Sodium-glucose cotransporter-2 inhibitors, T2D: Type 2 Diabetes Mellitus, CV: Cardiovascular, CKD: Chronic Kidney Disease, GLP-1RA: Glucagon-like peptide-1 receptor agonists, SC: Subcutaneous, MASH: Metabolic dysfunction-associated steatohepatitis

Table 1.2. HIV-Specific Considerations for Commonly used Antidiabetic Medication Classes

Antidiabetic Class	Considerations in PWH
Biguanides (Metformin)	**Drug-Drug Interactions** • Dolutegravir ↑ metformin concentration (via OCT2/MATE1 inhibition), potentially ↑ lactic acidosis risk • Monitor glycemic control and side effects if these medications are co-administered and be especially vigilant in patients with renal impairment to avoid lactic acidosis. • All NRTIs may also cause hyperlactinaemia, however older drugs carry the highest risk (zidovudine, stavudine and didanosine)
GLP-1 Receptor Agonists	**Benefits** • Significant weight loss similar to general population (benefit for patients with obesity and lipohypertrophy) • Potential benefit for PWH with cardiovascular, kidney, and liver disease (limited research) **Risks** • Potential muscle mass reduction; caution in patients with sarcopenia and lipoatrophy **Drug-Drug Interactions** • Minimal drug interaction risk; metabolized by endopeptidases. Theoretically, elevated gastric pH may affect absorption of atazanavir and oral rilpivirine (separate orally administered GLP-1 agonists intake by 4 hours before rilpivirine and 2–4 hours before atazanavir)
SGLT2 Inhibitors	**Benefits** • Potential benefit for PWH with cardiovascular disease, kidney disease, and heart failure (limited research) **Risks** • PWH may be at higher risk for infections (UTIs, mycotic infections, Fournier's gangrene); risks heightened if immune recovery is insufficient, or ART adherence is suboptimal **Drug-Drug Interactions** • UDP-glucuronosyltransferase enzyme inducers (e.g., ritonavir) ↓ canagliflozin levels • Dose adjustments for canagliflozin: increase from 100 mg to 200 mg daily; for eGFR ≥ 60 mL/min, it may be increased to 300 mg daily (not exceeding 200 mg for eGFR < 60 mL/min)

Sulfonylureas	**Risks** • Monitor for weight gain and hypoglycemia **Drug-Drug Interactions** • Protease inhibitors (e.g., ritonavir, nelfinavir) may ↓sulfonylurea levels via CYP2C9 induction; monitor closely
DPP-4i	**Drug-Drug Interactions** • Ritonavir (CYP3A4 inhibitor) may ↑ saxagliptin levels (clinical significance unknown since DPP-4i have a large safety window)
TZDs	**Risks** • Monitor for weight and fluid retention • Avoid in patients with HF, CKD, liver disease, and osteoporosis
Insulin	**Risks** • Monitor for hypoglycemia and weight gain

References: Cornish & Tseng, 2015[263]; Zino, 2023[238]; Sarkar & Brown, 2023[264]

Abbreviations: ART, antiretroviral therapy; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; NRTI, nucleoside reverse transcriptase inhibitor; SGLT2i, sodium–glucose cotransporter-2 inhibitors; TZD, thiazolidinedione; UGT, UDP-glucuronosyltransferase.

1.4 Review of Evidence on Novel Antidiabetic Medications in the General Population and People with HIV

The section summarizes current evidence on the effectiveness and safety of novel antidiabetic medications, specifically GLP-1RA and SGLT2 inhibitors, in managing the above discussed comorbidities in the general population. For PWH, evidence is more limited, particularly for kidney disease and depression.

1.4.1 Obesity

1.4.1.1 Evidence from the general population

Evidence from RCTs

The weight loss efficacy of the three FDA-approved GLP-1RA and GLP-1/GIP receptor agonist for obesity, liraglutide, semaglutide, and tirzepatide, has been extensively studied through various clinical trials in the general population.

Four large randomized double-blind placebo-controlled trials of liraglutide were done and they are part of the Satiety and Clinical Adiposity Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) program. The body weight loss in the four SCALE trials ranged from 5.7% to 8.0% with the 3.0 mg liraglutide. The four studies are summarized in Table 1.3.

Table 1.3. Liraglutide Weight Loss Trials: Summary of the SCALE Trials

Study	Participant Characteristics	N	Duration (weeks)	Weight Loss (%)	
				Liraglutide 3 mg	Placebo
SCALE Obesity and Prediabetes	Obesity or overweight with comorbidities	3,731	56	8.0%	2.6%
SCALE Diabetes	T2D	846	56	6.0%	2.0%
SCALE Maintenance	Individuals who lost ≥5% body weight during a 12-week low-calorie diet run-in	422	56	6.2%	0.2%
SCALE Sleep Apnea	Obesity and moderate to severe obstructive sleep apnea	359	32	5.7%	1.6%

Semaglutide has been evaluated in two major trial programs: one for obesity, the STEP (*Semaglutide Treatment Effect in People with obesity*) trials[217,221,265–269]and one for type 2 diabetes, the SUSTAIN (*Semaglutide Unabated Sustainability in Treatment of type 2 Diabetes*) trials. In the STEP trials, which focused on individuals with obesity or overweight, semaglutide showed impressive weight loss results. Participants receiving semaglutide experienced weight reductions of 9.6% to 16.0%, compared with 1.9% to 5.7% reductions in the placebo group. The proportion of participants achieving more than 10% weight loss was significantly higher in the semaglutide groups, with 69.1% in STEP 1 and 75.3% in STEP 3 trial, compared to much lower percentages in the placebo groups.[268] The STEP trials are summarized in Table 1.4. The SUSTAIN trials, targeting individuals with T2D, also demonstrated significant weight loss benefits with semaglutide. The weight loss achieved by the 0.5 and 1 mg subcutaneous doses of semaglutide in the SUSTAIN 1 through 11 trials ranged from -3.5 to -6.5 kg.[270–276] In a meta-analysis, semaglutide has been shown to produce significantly greater weight loss compared to liraglutide.[277]

Table 1.4. Semaglutide Weight Loss Trials: Summary of the STEP trials

Study	Participant Characteristics	N	Duration (Weeks)	Weight loss (%)		Proportion with >10% Weight Loss	
				Semaglutide	Placebo	Semaglutide	Placebo
STEP 1	Obesity or overweight without T2D	1961	68	-14.9%	-2.4%	69.1%	12.0%
STEP 2	Obesity or overweight with T2D	1210	68	-9.6%	-3.4%	45.6%	28.7%
STEP 3	Obesity or overweight without T2D, adjunct to intensive behavioral therapy	611	68	-16.0%	-5.7%	75.3%	27.0%
STEP 4	Obesity or overweight without T2D, after 20-week run-in with semaglutide	803	68	-7.9%	6.9%	79.0%	20.4%
STEP 5	Obesity or overweight without T2D	304	104	-15.2%	-2.6%	61.8%	13.3%
STEP 6	Obesity or overweight with or without T2D	401	68 weeks	-13.2%	-2.1%	61.0%	5.0%
STEP 8	Obesity or overweight without T2D	338	68 weeks	-15.8%	-1.9%	70.9%	15.4%

Tirzepatide, a novel GLP-1 and GIP receptor agonist, is the newest medication in this class and has been evaluated in two major trial programs: one for obesity (the SURMOUNT trials) and one for T2D (the SURPASS trials). SURMOUNT-1 which included 2,539 individuals with obesity or overweight without T2D, reported a dose-dependent weight loss ranging from 15% to 21% with tirzepatide compared to 3.1% with placebo over 72 weeks.[218] SURMOUNT-2, with 1,875 participants with obesity or overweight and T2D, showed a weight loss of 12% to 17% with tirzepatide compared to 2.5% with placebo.[278] Generally, people with diabetes tend to lose less weight compared to people without diabetes. The weight loss achieved by the various doses of

tirzepatide in the SURPASS trials ranged from -6.2 to -13.0 kg.[279–283] The SURMOUNT and SURPASS trials are summarized in Tables 1.5 and 1.6.

Table 1.5. Tirzepatide Weight Loss Trials: Summary of the SURMOUNT Trials

Study	Participant Characteristics	N	Duration (Weeks)	Weight loss (%)		Individuals with >10% Weight Loss	
				Tirzepatide	Placebo	Tirzepatide	Placebo
SURMOUNT-1	Obesity or overweight *without* T2D	2539	72	5 mg: -15% 10 mg: -20% 15 mg: -21%	-3.1%	85%	30%
SURMOUNT-2	Obesity or overweight *with* T2D	1875	72	5 mg: -12% 10 mg: -15% 15 mg: -17%	-2.5%	75%	20%

Table 1.6. Tirzepatide Diabetes Trials: The SURPASS Trials

Study	Participant Characteristics	N	Duration (Weeks)	Weight Loss (kg)	
				Tirzepatide	Comparator
SURPASS-1	T2D inadequately controlled with diet and exercise	478	40	5 mg: -7.0 10 mg: -7.8 15 mg: -9.5	-0.7 (Placebo)
SURPASS-2	T2D inadequately controlled with metformin	1879	40	5 mg: - 7.8 10 mg: -10.3 15 mg: -12.4	-6.2 (Semaglutide 1 mg)
SURPASS-3	T2D inadequately controlled with metformin ± SGLT2i	1444	52	5 mg: - 7.5 10 mg: -10.7 15 mg: -12.9	+2.3 (Insulin degludec)
SURPASS-4	T2D inadequately controlled with insulin glargine ± metformin	1995	52	5 mg: - 7.1 10 mg: -9.5 15 mg: -13.0	+1.9 (Insulin glargine)
SURPASS-5	T2D inadequately controlled with insulin glargine ± metformin	475	40	5 mg: -6.2 10 mg: -8.2 15 mg: -10.9	+1.7 (Placebo)

According to a network meta-analysis of RCTs involving 469 trials and over 220,000 patients, with a median follow-up of 6 months, the average difference in body weight reduction for SGLT2 inhibitors was about -1.92 kg (95% CI -2.23 to -1.62), and for GLP-1RA, it was approximately -1.45 kg (95% CI -1.72 to -1.18). This analysis did not include semaglutide, a newer GLP-1RA approved

for weight loss, which could explain the reason behind SGLT2 inhibitors leading to greater weight loss compared to GLP-1RA.[38]

Long-term RCTs and meta-analyses show that most patients regain 60–70% of lost weight within a year after stopping GLP-1RA therapy, regardless of the specific agent (semaglutide, liraglutide, tirzepatide) or treatment duration.[284–287] For example, in STEP-1 and STEP-4, semaglutide users regained ~68% of lost weight after one year, with similar trends for liraglutide and tirzepatide.[288,289]

Evidence from observational studies

A cohort study conducted by Lyu et al., using Electronic Health Record (EHR) data from Pennsylvania observed patients with diabetes who began treatment with different antidiabetic medications: SGLT2 inhibitors (906 patients), GLP-1RA (782 patients), DPP4 inhibitors (1881 patients), and sulfonylureas (3255 patients). When compared to sulfonylureas, the newer antidiabetic drugs showed significant weight loss, including -3.2% (CI: -3.8% to -2.6% per year) for SGLT2 inhibitors, -2.9% (CI: -3.6% to -2.3% per year) for GLP-1RA, and -1.7% (CI: -2.1% to -1.3% per year) for DPP4 inhibitors. Both SGLT2 inhibitors and GLP-1RA also demonstrated significant weight loss compared to DPP4 inhibitors. Similar to the network meta-analysis mentioned above only a few patients in the GLP-1RA group were on semaglutide.[290]

Real-world evidence for semaglutide in the general population consists of a post hoc analysis of four Semaglutide Real-world Evidence (SURE) studies (SURE Canada, Denmark/Sweden, Switzerland and UK) including 1,212 patients with T2D and a mean BMI of 35 kg/m^2 treated with lower doses of subcutaneous semaglutide for approximately 30 weeks (52 weeks permissible in UK study) showed a significant decrease of body weight of 4.7 kg.[291] In a retrospective study

conducted by Ghusn et al., involving 175 patients who were overweight or obese, the effects of semaglutide on weight loss were examined. After 6 months of treatment with semaglutide, the patients, on average, experienced a weight loss of 10.9% or 12.3 kg. Importantly, 44% of the patients in the study were administered higher doses of semaglutide (1.7 mg or 2.4 mg).[292]

1.4.1.2 Evidence from people with HIV

Most clinical trials of GLP-1RA were conducted in populations without HIV and with limited comorbidities, which may limit generalizability to PWH, who often have a high burden of metabolic diseases and are on polypharmacy, including ART associated with weight gain. Evidence of weight loss associated with GLP-1RA is relatively new and limited among PWH (mainly coming from small clinical trials and small observational studies), and there is currently no evidence for the potential weight loss effects of SGLT2 inhibitors in this population. The RCTs and observational studies on the impact of GLP-1RA among PWH are summarized below.

An observational study conducted by our group using data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, found that treatment with semaglutide resulted in significant weight loss among 222 PWH. At one year, the average body weight loss was 6.47 kg (95% CI: -7.71 to -5.23), and the average percentage of body weight lost was 5.72% (95% CI: -6.86 to -4.58).[293]

A recent retrospective single-center cohort study among PWH included 225 patients taking GLP-1RA with an average follow up of 13 months, showed that GLP-1RA therapy resulted, on average, in a loss of 5.4 kg and decrease in BMI by 1.8 kg/m^2. Moreover, higher baseline BMI, treatment duration of GLP-1RA therapy greater than 6 months, and use of tirzepatide were significantly more likely to be associated with >5% weight loss.[294]

In a small retrospective chart review by Lloyd et al., the effects of GLP-1RA on body weight were examined in noninfected diabetics (n = 30) and PWH and diabetes (PWHD, n = 15). The study found that noninfected diabetics participants experienced a weight loss of only −1.7 kg, whereas PWHD participants had a weight loss of −10.4 kg. [295]

Eckard et al. conducted a single-site, randomized, double-blind, placebo-controlled trial to evaluate the effects of semaglutide in PWH who had well-controlled HIV, a BMI ≥25 kg/m², and lipohypertrophy, but who did not have diabetes. Over 32 weeks, semaglutide significantly reduced body weight by 10.4% and total body fat by 18.9%. Abdominal visceral adipose tissue (VAT) decreased by 30.6% and abdominal subcutaneous adipose tissue (SAT) decreased by 11.2% and trunk fat saw a reduction of 21.6%. However, the study revealed unexpected findings: semaglutide did not reduce liver or pericardial fat. Additionally, there was a 5.7% loss in lean mass.[239,296]

Another trial, the SLIM LIVER study, was a phase 2b, single-group, open-label trial of semaglutide in PWH with central adiposity, insulin resistance or prediabetes, and steatotic liver disease (SLD, defined as ≥5% of liver volume as intrahepatic triglyceride). The study's main outcome investigated the impact of semaglutide on intrahepatic triglycerides. Participants received a low dose of subcutaneous semaglutide, gradually increased to 1 mg/week by week 4, for a total of 24 weeks. Average weight loss over 24 weeks was 7.8 kg (8.1%). The largest reductions were seen in women, both Hispanic and non-Hispanic whites, and participants aged 40 years or older.[297]

Overall, the available evidence suggests that GLP-1RA, particularly semaglutide, can produce substantial weight loss and reductions in abdominal fat, including visceral and subcutaneous adipose tissue, in PWH, which may improve cardiometabolic risk. [298] Weight loss may also involve

modest reductions in lean muscle mass, which is especially relevant in PWH who are at increased risk of sarcopenia, sarcopenic obesity, and frailty.[150,219,240] Although small studies indicate that these lean mass losses do not appear to substantially impair physical function, [239,299] larger and longer-term studies are needed to fully understand the effects on muscle mass, strength, and overall physical function in this population.

1.4.2 Kidney Disease

1.4.2.1 Evidence from the general population

In the general population, there is evidence from RCTs showing the benefits of GLP-1RA and SGLT2i in improving kidney outcomes, which are discussed below. In light of this evidence, current American Diabetes Association (ADA) guidelines recommend SGLT2 inhibitors for patients with diabetic CKD (eGFR ≥20 ml/min/1.73 m^2) and recommend a GLP-1RA if SGLT2 inhibitors are not tolerated or contraindicated.[47,300] And according to the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[257] SGLT2i are recommended for patients with T2D, CKD, and an eGFR of ≥20 ml/min/1.73 m^2. And in patients with T2D and CKD who have not achieved glycemic targets despite use of metformin and SGLT2i treatment, or who cannot tolerate these medications, a GLP-1RA with CV benefit is recommended. The GLP-1RA are recommended only for people who have diabetes, while SGLT2 inhibitors are recommended for people with CKD with or without diabetes.

RCTs of GLP-1RA

Preliminary evidence on the renal benefits of GLP-1RA was derived from cardiovascular outcome trials (CVOTs), which were large, multicenter, double blind, placebo-controlled RCTs designed to investigate the CV safety of GLP-1RA. Notable examples of CVOTs include ELIXA,[301] LEADER,[302,303] SUSTAIN-6,[270] EXSCEL,[304] REWIND[305] which are summarized in Table 1.7.

A meta-analysis of GLP-1RA CVOTs showed that GLP-1RA treatment reduced the risk of a composite kidney outcome, which included new-onset macroalbuminuria (MA), doubling of serum creatinine or a decline in eGFR of at least 40 percent, kidney replacement therapy, or death

due to kidney disease, by 21 percent compared to placebo (HR 0.79, 95% CI 0.73 to 0.87). [306] This benefit was primarily driven by a reduction in albuminuria. Most trials reported a significant reduction in new-onset MA, except for ELIXA and EXSCEL, which did not achieve statistical significance. In ELIXA, the effect of lixisenatide on urine albumin-to-creatinine ratio (UACR) progression became apparent only after adjustment for HbA1c. [301] ELIXA also differed from other trials because all participants had acute coronary syndrome (ACS), a population at higher risk of recurrent cardiovascular events and mortality.[301] Moreover, lixisenatide is short-acting, with a plasma half-life of around 3 hours,[307] and in the trial, it was administered once daily, which may not have been sufficient for prolonged GLP-1 receptor inhibition.

A recent trial of semaglutide, SELECT,[308] was not included in the meta-analysis above or Table 1.7. This trial is a CVOT in patients with preexisting CVD and overweight or obesity but without diabetes. Published in December 2023, SELECT provided insights into semaglutide's renal effects. The study enrolled a total of 17,604 patients, with 8,803 assigned to receive semaglutide 2.4 mg and 8,801 to receive placebo. The mean (± SD) duration of exposure to semaglutide or placebo was 34.2 ± 13.7 months, and the mean follow-up duration was 39.8 ± 9.4 months. A secondary outcome was a composite renal endpoint that included death from renal causes, initiation of long-term renal replacement therapy (dialysis or transplantation), onset of a persistent eGFR lower than 15 ml/min/1.73 m^2, a persistent 50% reduction in eGFR relative to baseline, or the onset of persistent macroalbuminuria (urinary albumin-to-creatinine ratio >300 mg/g). In this composite endpoint, semaglutide was associated with a lower incidence compared to placebo, with 155 (1.8%) cases in the semaglutide group vs 198 (2.2%) in the placebo group (HR 0.78 [95% CI: 0.63 to 0.96]).[308]

Renal oriented trials were designed specifically to investigate the efficacy and safety of GLP-1RA in patients with T2D and CKD. Notable renal-oriented trials include LIRA-RENAL[309], HARMONY-8, [310] AWARD-7,[311] PIONEER 5,[312] and FLOW[41] which are summarized in Table 1.8. These trials, except for FLOW, had a primary outcome of change in HbA1c, so their main outcome was not to assess the reduction in kidney disease progression.

The FLOW trial[41] is the first dedicated trial of patients with diabetes and CKD involving a kidney primary outcome. The FLOW trial of semaglutide was published in May 2024. In the FLOW trial, patients with T2D and CKD (eGFR of 50 to 75 ml/min/1.73 m² with a urinary albumin-to-creatinine ratio between 300 and 5,000 mg/g, or an eGFR of 25 to <50 ml/min/1.73 m² with a urinary albumin-to-creatinine ratio between 100 and 5,000 mg/g) were included. Participants were randomly assigned to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or a placebo. The study included 3,533 participants, with 1,767 in the semaglutide group and 1,766 in the placebo group. The median follow-up was 3.4 years. The primary outcome measured was major kidney disease events, defined as the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml/min/1.73 m²), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. Results indicated a 24% reduction in the risk of primary-outcome events in the semaglutide group compared to the placebo group, with 331 events occurring in the semaglutide group vs 410 in the placebo group (HR 0.76; 95% CI: 0.66 to 0.88; P = 0.0003). Additionally, the mean annual eGFR slope in the semaglutide group was less steep, indicating a slower rate of decline, by 1.16 ml/min/1.73 m² compared to the placebo group (P < 0.001).[41]

Table 1.7. Cardiovascular Outcome Trials of GLP-1RA

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND
Drug vs. comparator	Lixisenatide vs. placebo	Liraglutide vs. placebo	Semaglutide vs. placebo	Exenatide vs. placebo	Dulaglutide vs. placebo
N	6068	9340	3297	14752	9463
Population	Adults with T2D and a history of CV events (recent acute coronary syndrome, myocardial infarction, or unstable angina)	Adults with T2D and high CV risk	Adults with T2D and either a history of CVD or multiple CV risk factors	Adults with T2D and a history of CVD or at high risk for CV events	Adults with T2D and either CVD or multiple CV risk factors
Main Renal Composite Outcome					
Definition	New-onset macroalbuminuria (MA) (UACR > 300 mg/g) MA	New-onset MA; persistent doubling of SCr (eGFR < 45 ml/min/1.73 m^2); renal-replacement therapy; renal death	New-onset MA; persistent doubling of SCr (eGFR < 45 ml/min/1.73 m^2); continuous renal-replacement therapy; renal death	New-onset MA; ≥40% eGFR decrease; renal-replacement therapy; renal death	New-onset MA; ≥30% eGFR decrease; renal-replacement therapy
HR (95% CI)	0.81 (0.66–0.99)	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.88 (0.76–1.01)	0.85 (0.77–0.93)
Secondary Renal Outcomes (HR [95% CI])					
Worsening kidney function	1.16 (0.74–1.83)	0.89 (0.67–1.19)	1.28 (0.64–2.58)	0.88 (0.74-1.05)	0.70 (0.57–0.85)
New-onset MA	0.81 (0.66–0.99)	0.74 (0.74–0.91)	0.54 (0.37–0.77)	143/6456 vs. 173/6458	0.77 (0.68–0.87)
Renal-replacement therapy	3/2702 vs. 7/2793	0.87 (0.61–1.24)	0.91 (0.40–2.07)	55/7344 vs. 65/7389	0.75 (0.39–1.44)
Renal death	-	1.59 (0.52–4.87)	-	5/7356 vs. 5/7396	-

Abbreviations: T2D: Type 2 Diabetes, CV: Cardiovascular, MA: Macroalbuminuria, UACR: Urinary Albumin-to-Creatinine Ratio, SCr: Serum Creatinine, eGFR: Estimated Glomerular Filtration Rate, HR: Hazard Ratio

Table 1.8. Renal Oriented Trials of GLP-1RA

Characteristic/Outcome	LIRA-RENAL	HARMONY 8	AWARD-7	PIONEER 5
Drug vs. Comparison	Liraglutide vs. placebo	Albiglutide vs. sitagliptin	Dulaglutide 0.75 Dulaglutide 1.5 Insulin glargine	Oral semaglutide vs. placebo
N	277	495	577	324
Study Duration (Weeks)	26	52	26	26
Mean Age (Years)	67	63.3	64.6	70
Female (%)	49.5	46.3	47.6	52
Mean Diabetes Duration (Years)	15	11.2	18.1	14
Mean HbA1c (%)	8	8.2	8.6	8
Mean eGFR (ml/min/1.73 m²)	45.5	–	36	48
eGFR <60 ml/min/1.73 m² (%)	100	49.3	94.6	100
UACR (mg/g)	62.2	–	214.3	16
Secondary/Safety Endpoints				
Median eGFR Ratio (end of study/baseline)	Liraglutide 0.99; placebo 1.01 ETR = 0.98 (95% CI 0.94–1.02, p = 0.36)	-	-	Semaglutide 1.02(0.27–1.96); placebo 1.00 (0.68–2.17)
Mean UACR Ratio (end of study/baseline)	Liraglutide 0.87; placebo 1.05 ETR = 0.83 (95% CI 0.62–1.10, p = 0.19)	-	-	Semaglutide 0.86 (0.04–56.71); placebo 1.19 (0.01–79.59)
eGFR Difference (end of study)	-	-	33.8 ml/min/1.73 m² (p = 0.009 vs. insulin glargine)	34.0 ml/min/1.73 m² (p = 0.005 vs. placebo)
UACR Difference (end of study)	-	-	−20.1% (95% CI −33.1 to −4.6)	−22.5% (95% CI −35.1 to −7.5)

Abbreviations: eGFR: Estimated Glomerular Filtration Rate, UACR: Urinary Albumin-to-Creatinine Ratio, HbA1c: Hemoglobin A1c, ETR: Estimated Treatment Ratio.

RCTs of SGLT2 inhibitors

The initial CVOTs, EMPA-REG, CANVAS, DECLARE-TIMI 58[313–315] not only showed that SGLT2i are effective in reducing CV mortality and hospitalization for heart failure in patients with and without diabetes, but secondary endpoints from these trials indicated up to a 40% reduction in the risk of progression of kidney disease.[313–316] These initial studies primarily included patients with relatively normal kidney function and minimal albuminuria. Following these findings, subsequent RCTs were specifically designed to assess primary kidney outcomes, targeting patients with varying levels of baseline kidney impairment and more significant albuminuria. Table 1.9 summarizes the renal oriented RCTs which include CREDENCE,[317] DAPA-CKD,[318] and EMPA-KIDNEY.[319]

An updated systematic review and meta-analysis of SGLT2 inhibitors trials included 13 trials involving over 90,000 participants. Baseline eGFR ranged from 37-85 mL/min/1.73 m^2 with 83% having diabetes. The results showed that compared with placebo, SGLT2 inhibitor users had a reduced risk of kidney disease progression by 37% (RR 0.63, 95% CI 0.58–0.69) irrespective of diabetes status. SGLT2 inhibitors reduced the risk of acute kidney injury by 23% (0.77, 0.70–0.84) and the risk of cardiovascular death or hospitalization for heart failure by 23% (0.77, 0.74–0.81). SGLT2 inhibitors also reduced the risk of cardiovascular death (0.86, 0.81–0.92) but did not significantly reduce the risk of non-cardiovascular death (0.94, 0.88–1.02).[320]

Table 1.9. Renal Oriented Trials of SGLT2 inhibitors

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Drug vs. Comparator	Canagliflozin 100 mg daily vs placebo	Dapagliflozin 10 mg daily vs placebo	Empagliflozin daily vs placebo
N	4,401	4,304	6,609
Population Characteristics	T2D and CKD On RAAS blockade Excluded suspected non-diabetic CKD	With/without T2D On RAAS blockade Excluded PCKD, T1DM, lupus, recent immunosuppression	with/without T2D On RAAS blockade Excluded PCKD
Baseline eGFR (mL/min/1.73 m²)	30 to <90	25 to <75	20 to <45 or 45 to <90 with albuminuria
Mean (SD) eGFR, mL/min/1.73 m²	56 (18)	43 (12)	37 (14)
Albuminuria (mg/g)	>300-5,000	200-5,000	Any level of albuminuria if eGFR 20 to <45; at least 200 if eGFR 45 to <90
Median (IQR) UACR, mg/g	927 (463-1,833)	949 (477-1,885)	329 (49-1,069)
% Without diabetes	0%	32%	54%
Median (IQR) follow-up, years	2.62 (0.02-4.53)	2.4 (2.0-2.7)	2.0 (1.5-2.4)
Primary Outcome	Composite of ESKD, doubling of SCr from baseline, or death from renal or CV causes	Composite of any of a decline of at least 50% in eGFR, onset of ESKD, or death from renal or CV causes	First occurrence of kidney disease progression or death from CV causes
Primary Outcome Result (HR, 95% CI)	0.70 (0.59-0.82)	0.61 (0.51-0.72)	0.72 (0.64-0.82)

Abbreviations: eGFR: Estimated Glomerular Filtration Rate, RAAS: Renin-Angiotensin-Aldosterone System, PCKD: Polycystic Kidney Disease, T1DM: Type 1 Diabetes Mellitus, UACR: Urinary Albumin-to-Creatinine Ratio, ESKD: End-Stage Kidney Disease, SCr: Serum Creatinine, CV: Cardiovascular

Evidence from observational studies

There is significant real-world evidence showing that SGLT2 inhibitors improve kidney outcomes in the general population. Key observational studies are summarized below.

In a large multinational observational cohort study known as CVD-REAL 3, led by Heerspink[321] the research focused on new users of SGLT2 inhibitors and other glucose-lowering medications. Data were sourced from claims, medical records, and national registries in Israel, Italy, Japan, Taiwan, and the UK. One to one propensity score matching was performed for users of SGLT2i and other glucose lowering medications. The primary outcome of interest was the rate of eGFR decline. The study included a total of 35,561 episodes of treatment initiation in both the SGLT2 inhibitor and other glucose-lowering drug groups, involving 65,231 patients. Results showed that the initiation of SGLT2 inhibitors was associated with a significant reduction in the rate of eGFR decline (difference in slope between SGLT2 inhibitors and other glucose-lowering drugs was 1.53 mL/min per 1.73 m^2 per year (95% CI 1.34 to 1.72)). The initiation of SGLT2 inhibitors was associated with a 51% lower risk of a composite outcome (HR 0.49; 95% CI 0.35 to 0.67), which included a 50% decline in eGFR or progression to end-stage kidney disease (ESKD).[321]

In a study conducted by Xie et al,[322] U.S. veterans who were initiated on different classes of antidiabetic medications were followed up to three years. The primary objective was to assess the risk of a composite outcome, which included a decline in eGFR of more than 50%, ESKD, or all-cause mortality. Comparative analysis revealed that individuals treated with SGLT2i, GLP-1RA, and DPP-4 inhibitors exhibited a reduced risk of the composite outcome when compared to those treated with sulfonylureas (HR 0.68 [95% CI 0.63, 0.74], 0.72 [0.67, 0.77], and 0.90 [0.86, 0.95], respectively). Although no statistically significant difference in risk was detected between the

SGLT2i and GLP-1RA treatment groups (HR 0.95; 95% CI 0.87 to 1.04), it is noteworthy that both SGLT2i and GLP-1 exhibited a reduced risk of the composite outcome when compared to DPP-4 inhibitors. For SGLT2i: HR 0.76; 95% CI 0.70 to 0.82 and for GLP-1RA: HR 0.79; 95% CI 0.74 to 0.85.[322]

Using UK primary care electronic health records, Perez et al.,[323] followed two cohorts of patients with T2D prescribed metformin: SGLT2 inhibitors (N=12 978) and a matched comparator of patients not using an SGLT2i at the start of follow-up (N=44 286). Results showed that SGLT2i were associated with a reduced risk of severe renal disease (HR 0.55, 95% CI: 0.46 to 0.67) and all-cause mortality (HR 0.56, 95% CI: 0.49 to 0.63), with risk reductions similar irrespective of baseline chronic kidney disease.[323]

In another study, Lui et al.,[324] used a real-world population-based database from the Hong Kong Hospital Authority. They compared individuals who initiated treatment with SGLT2i to those who initiated treatment with GLP-1RA propensity-score matched 1:1. The primary outcome of interest was a composite of kidney-related events, which included a sustained decline in eGFR of at least 50%, ESKD, incident macroalbuminuria, and kidney-related mortality. The secondary outcome was the rate of eGFR decline. In the study, a total of 2,551 new users of SGLT2 inhibitors were analyzed and matched with an equal number of new users of GLP1 receptor agonists. At baseline, the average age of the participants was 56.2 years, with an average eGFR of 78.0 mL/min/1.73m^2, and 11.9% of them had macroalbuminuria. Over a median follow-up period of 13 months (with an IQR of 5 to 27 months), SGLT2 inhibitor users exhibited a reduced risk of the composite kidney-related outcomes (HR 0.77, 95% CI 0.62–0.96). This reduction was primarily due to a decrease in the incidence of ESKD (HR = 0.53, p = 0.01). SGLT2 inhibitor users also displayed a tendency

towards a decreased risk of developing incident macroalbuminuria (HR = 0.74, p = 0.05). Additionally, the study found that SGLT2 inhibitor users experienced a slower decline in eGFR compared to GLP1 receptor agonist users (SGLT2i: -1.19 mL/min/1.73m^2/year vs. GLP1RA: -1.95 mL/min/1.73m^2/year, p < 0.01).[324]

A Scandinavian cohort study using an active comparator, new-user design from registry data from Sweden, Denmark, and Norway included 38,731 new users of GLP-1 receptor agonists (92.5% on liraglutide) propensity score matched 1:1 to DPP-4 inhibitors.[325] The main outcome was serious renal events, a composite including renal replacement therapy, death from renal causes, and hospitalization for renal events. Initiators of GLP-1RA had a lower risk of a composite renal endpoint (HR 0.76, 95% CI 0.68-0.85). Secondary outcomes were the individual components of the main outcome. GLP-1RA initiators had a lower risk of renal replacement therapy (HR 0.73, 95% CI 0.62–0.87) and hospitalization for renal causes (HR 0.73, 95% CI 0.65–0.83).[325]

1.4.2.2 Evidence from people with HIV

To date, no studies have specifically evaluated the renal effects of GLP-1 agonists or SGLT2 inhibitors among PWH. This represents an evidence gap given the high burden of kidney disease in this population and the potential for HIV-specific factors (e.g., inflammation, ART-related nephrotoxicity) to modify medication effects. Future research is needed to assess whether the renal benefits observed in the general population translate to PWH, and whether this population may be more susceptible to the acute hemodynamic effects of SGLT2 inhibitors.

1.4.3 Depression and related mental health outcomes

1.4.3.1 Evidence from the general population

This section reviews the current evidence from randomized controlled trials, observational studies, and pharmacovigilance studies in the general population regarding the psychiatric safety of GLP-1RA. It focuses on their effects on depression and suicidality among people with overweight, obesity, and/or type 2 diabetes. Overall, the evidence on GLP-1RA and mental health is mixed; however, most high-quality studies suggest neutral or potentially beneficial effects on psychiatric outcomes, with no consistent signals of harm.

Evidence from RCTs

Multiple meta-analyses of RCTs indicate that GLP-1RA do not increase the risk of psychiatric adverse events or depressive symptoms. For example, Chen et al.[326] conducted a systematic review and meta-analysis of six studies involving 2,071 participants (mean age ~58 years), primarily patients with type 2 diabetes. The GLP-1RA studied included exenatide and liraglutide. Depression was measured using validated scales such as the Montgomery-Åsberg Depression Rating Scale and Beck's Depression Inventory. Compared to placebo or other antidiabetic treatments, GLP-1RA therapy was associated with a small but statistically significant reduction in depressive symptoms, with a standardized mean difference of –0.12 (95% CI, –0.21 to –0.03; $p < 0.01$). However, limitations include the small number of studies, short durations (typically weeks to months), and the fact that depression was not a primary endpoint in these RCTs. Furthermore, populations were heterogeneous, including a study with Parkinson's disease patients, and different depression scales and comparators were used.[326]

Similarly, a large meta-analysis by Pierret et al.[327] reviewed 80 clinical trials with over 100,000 patients and found that GLP-1RA did not increase the risk of psychiatric side effects, such as depression. In fact, treatment with GLP-1RA was linked to small but meaningful improvements in eating behaviors, such as better control over emotional and restrained eating, and in quality of life, including both mental and physical health, as well as diabetes- and weight-related well-being.[327]

Further support comes from post hoc analyses of the STEP trials, which evaluated once-weekly semaglutide 2.4 mg in 3,681 adults with overweight or obesity and found no clinically meaningful differences in depressive symptoms or suicidality compared to placebo.[328] Baseline mean Patient Health Questionnaire-9 (PHQ-9) scores were low (~2.0), indicating minimal depression. Semaglutide treatment yielded a small but statistically significant reduction in PHQ-9 scores compared with placebo (mean difference −0.56; 95% CI, −0.81 to −0.32; $p < 0.001$). Rates of suicidal ideation or behavior were low (<1%) and balanced between groups.[328]

It is important to note that the RCTs assessing psychiatric outcomes with GLP-1RA were primarily designed to evaluate glycemic control or weight loss, with depression and other mental health effects considered only as secondary or exploratory endpoints. Consequently, these trials were generally underpowered to detect significant changes in psychiatric symptoms. Moreover, there was considerable heterogeneity in study populations and the depression assessment tools used, which complicates the synthesis and interpretation of findings. Also, individuals with known major psychiatric disorders or moderate-to-severe depression were typically excluded from these trials, limiting the generalizability of results to patients with more severe mental health conditions.

Evidence from observational studies

Real-world observational studies investigating the psychiatric safety of GLP-1RA have yielded generally reassuring findings, with several suggesting protective or neutral effects, though a few report possible increased risks.

For example, Wang et al.[329] conducted a large retrospective cohort study using US TriNetX data to assess the risk of suicidal ideation associated with semaglutide in two distinct cohorts: individuals with overweight or obesity (N = 105,566) and those with type 2 diabetes (N = 55,452). In both populations, semaglutide users had significantly lower risks of incident and recurrent suicidal ideation compared to users of other anti-obesity or antidiabetic medications. In the overweight/obesity cohort, the aHR for incident suicidal ideation was 0.27 (95% CI, 0.20–0.36), while in the type 2 diabetes cohort, it was 0.36 (95% CI, 0.25–0.53). However, the study had notable limitations. It did not use a new-user design, raising concerns about immortal time bias. The comparator groups included drugs such as topiramate, phentermine, bupropion, and naltrexone, which are either associated with increased risks of depression and suicidality or are prescribed for populations with underlying psychiatric comorbidities, introducing confounding by indication. Furthermore, the study lacked data on suicide deaths, which limited its ability to assess completed suicides, and no outcome validation using clinical diagnoses was reported.

Similarly, Tang et al.[330] emulated a target trial using US Medicare claims data from 2014 to 2020 to examine incident depression risk in older adults (≥66 years) with type 2 diabetes initiating GLP-1RA versus SGLT2 inhibitors or DPP-4 inhibitors. Compared with DPP-4 inhibitors, GLP-1RA use was associated with a modestly reduced risk of depression (HR 0.90, 95% CI, 0.82–0.98). No significant difference was observed when compared to SGLT2 inhibitors (HR 1.07, 95% CI, 0.98–

1.18). While methodologically rigorous with propensity score matching, the study is limited by residual confounding, use of administrative data without validated depression diagnoses, and limited generalizability to younger populations.

Additional support comes from a retrospective cohort study by Tsai et al[331] which included 53,456 patients with diabetes in Taiwan and used claims data from the National Health Insurance Research Database (NHIRD). Over a mean follow-up of 2.6 years for GLP-1RA users and 2.0 years for non-users, GLP-1RA (Liraglutide, Dulaglutide, Exenatide) use was associated with a lower risk of incident depression and/or anxiety, with a hazard ratio of 0.80 (95% CI, 0.67 to 0.95).

Consistent with these studies, Wium-Andersen et al.[332] conducted a nested case-control study using Danish national registries, including 73,869 patients with type 2 diabetes, where they assessed the association between GLP-1RA use and a composite outcome of depression diagnosis or antidepressant initiation. The odds ratio for GLP-1RA use versus non-use was 0.88 (95% CI, 0.80–0.97), indicating a modest protective effect. However, given the study's observational nature, potential residual confounding and measurement error in capturing depression diagnoses or medication initiation remain limitations.

Some observational studies reported null findings. For instance, Shapiro et al.[333] conducted a large, population-based active comparator cohort study using UK Clinical Practice Research Datalink (CPRD) data linked with hospital and mortality records to evaluate whether GLP-1RA use is associated with an increased risk of suicidality, including suicidal ideation, self-harm, and suicide, compared to DPP-4 inhibitors or SGLT2 inhibitors among patients with type 2 diabetes.

The study followed two cohorts: 36,082 GLP-1RA users versus 234,028 DPP-4 inhibitor users (median follow-up 1.3 and 1.7 years, respectively), and 32,336 GLP-1RA users versus 96,212 SGLT2 inhibitor users (median follow-up 1.2 years in both groups). Crude analyses initially suggested a higher incidence of suicidality among GLP-1RA users in both comparisons (hazard ratios [HRs] 2.08 and 1.60, respectively). However, after adjustment for confounding factors using propensity score weighting and Cox proportional hazards models, these associations were no longer significant (adjusted HR 1.02, 95% CI 0.85–1.23 for GLP-1RA vs DPP-4; adjusted HR 0.91, 95% CI 0.73–1.12 for GLP-1RA vs SGLT2i). Similar null results were observed when suicidal ideation, self-harm, and suicide were examined individually. It should be noted that this study included only patients with diabetes, which may limit generalizability.

Similarly, Ueda et al.[334] conducted a large binational cohort study using nationwide registry data from Sweden and Denmark (2013–2021) to evaluate psychiatric safety outcomes among users of GLP-1RA compared to SGLT2 inhibitor users. The study included 124,517 adults initiating GLP-1RA, mainly liraglutide (50%) and semaglutide (41%), and 174,036 initiating SGLT2 inhibitors, with a mean follow-up of 2.5 years. During this period, there were 77 suicide deaths among GLP-1RA users and 71 among SGLT2 inhibitor users, corresponding to weighted incidence rates of 0.23 versus 0.18 events per 1000 person-years, respectively. The hazard ratio for suicide death alone was 1.25 (95% CI, 0.83–1.88), indicating no statistically significant increased risk with GLP-1RA use. For the composite outcome of suicide death and nonfatal self-harm, GLP-1RA use was associated with a modestly reduced risk compared to SGLT2 inhibitors (HR 0.83; 95% CI, 0.70–0.97). Additionally, there was no meaningful difference in the risk of incident depression or anxiety-related disorders between groups (HR 1.01; 95% CI, 0.97–1.06). These findings suggest

that GLP-1RA use is not associated with an increased risk of suicide death, self-harm, or incident mood and anxiety disorders. However, given the rarity of suicide events, small absolute differences in risk cannot be definitively ruled out.

Additionally, Gamble et al.[335] analyzed data from the UK Clinical Practice Research Datalink (CPRD) in a cohort of 16,910 adults with type 2 diabetes, comparing GLP-1RA and sulfonylurea users. Over a median follow-up of approximately one year, no significant difference was observed in the risk of new-onset depression or self-harm (aHR 1.25, 95% CI, 0.63–2.50). Depression and self-harm were identified via diagnostic codes, which may underestimate true incidence.

In a study by Her et al.,[336] 16,822 adults starting semaglutide for weight management were compared with 11,986 users of other weight-loss drugs over six months, showing no increase in the risk of suicidal thoughts (0.08% vs. 0.05%) or suicidality (0.08% vs. 0.07%). However, because these events were rare and identified using ICD-10 diagnosis codes, which may miss or underreport some suicide-related cases, the true risk could be higher, and further studies are needed to confirm these findings.[336]

In contrast to the above studies, a large cohort study by Kornelius et al.,[337] using post marketing data from 2015 to 2023 reported increased psychiatric risks with GLP-1RA use. After 1:1 propensity score matching, 162,253 patients using liraglutide or semaglutide were compared to matched non-users. The study reported a 98% increased risk of any psychiatric disorder, with particularly elevated risks for major depression (195%), anxiety (108%), and suicidal behavior (106%). While striking, these findings require cautious interpretation, particularly because they

were derived from post-marketing data, which may be subject to confounding and reporting biases.

In a more recent new-user active comparator study by Chang el.,[338] 25,704 new GLP-1RA users were compared with matched 25,704 SGLT2i users among overweight or obese adults with type 2 diabetes, showing a higher incidence of depression with GLP-1RA (17.0% vs. 14.8%; hazard ratio 1.09, 95% CI 1.04–1.14), particularly in those aged ≥65 years, while GLP-1RA use was associated with lower all-cause mortality (HR 0.74, 95% CI 0.63–0.88).[338]

Overall, the current body of evidence from observational research suggests that GLP-1RA are not consistently associated with increased psychiatric risk in the general population. If anything, they may confer modest benefits on depressive symptoms or quality of life. However, interpretation of these findings must account for several limitations inherent to observational designs. Confounding by indication is a concern, as GLP-1RA are typically prescribed to individuals with obesity, diabetes, or cardiometabolic comorbidities, conditions themselves linked to depression and suicidality, potentially biasing associations in either direction. Confounding by disease severity may also occur if patients with more advanced metabolic or psychiatric illness are preferentially prescribed or excluded from GLP-1RA. Residual confounding from unmeasured factors such as socioeconomic stressors, or other life stressors further limits causal inference. In addition, misclassification bias is likely, as many studies relied solely on administrative data using ICD codes to define psychiatric outcomes, which tend to capture only more severe cases (e.g., suicide attempts requiring medical attention) while underestimating milder or unreported events. Finally, immortal time and selection biases, especially in non–new-user designs or when loss to follow-up is substantial, may distort risk estimates.[339–342] Taken together, while the cumulative

evidence remains broadly reassuring, these methodological challenges highlight the need for future well designed studies with careful control of confounding to more definitively establish the psychiatric safety profile of GLP-1RA.Pharmacovigilance analyses have further contributed to safety concerns. Schoretsanitis et al.[343] conducted a disproportionality analysis using the World Health Organization's global adverse drug reaction database to evaluate suicidal and self-injurious events associated with semaglutide and liraglutide. Among cases reported up to August 2023, semaglutide, but not liraglutide, showed a significant signal for suicidal ideation, with a reporting odds ratio (ROR) of 1.45 (95% CI, 1.18–1.77). This signal remained significant in patients also using antidepressants or benzodiazepines and when compared with other medications such as dapagliflozin, metformin, and orlistat. The authors concluded that semaglutide-associated suicidal ideation requires urgent further investigation. Additionally, Katranski et al.[344] conducted a pharmacovigilance analysis to investigate psychiatric adverse events (AEs) associated with GLP-1 analogues using national reporting databases from the US, Canada, and Australia. Disproportionality analyses calculated reporting odds ratios (RORs) for psychiatric AEs linked to various GLP-1RA. The study found significant associations between semaglutide and depressive symptoms (ROR = 6.24), panic attacks (ROR = 1.46), and suicidal ideation (ROR = 2.58) in the FAERS database. Liraglutide was associated with depression (ROR = 1.68) in the Canadian dataset. Dulaglutide showed increased reports of eating disorders (ROR = 1.47) and insomnia (ROR = 2.93). The authors conclude that GLP-1 analogues, especially semaglutide and liraglutide, are linked to notable adverse psychiatric events, highlighting the need for further research to clarify these associations and underlying mechanisms, particularly in patients with pre-existing psychiatric conditions.

McIntyre et al. initially analyzed data from the FAERS spanning 2005 to 2023 to assess suicidality associated with GLP-1RA.[345] Their findings revealed disproportionate reporting of suicidal ideation and depression with suicidal features for semaglutide and liraglutide, but no increased reporting for suicidal behavior, suicide attempts, or completed suicides across any GLP-1RA. After adjusting for potential confounders, the authors concluded there was no evidence to support a causal link between GLP-1RA use and suicidality based on the spontaneous reports. Building on this, a subsequent study by McIntyre et al.[346] using the World Health Organization's VigiBase database through January 2024 found significantly increased reporting odds ratios (RORs) for suicidal ideation and combined depression/suicidality for semaglutide, liraglutide, and tirzepatide. However, RORs for suicide attempts and completed suicides were significantly decreased for several GLP-1RA, including semaglutide and liraglutide. The authors emphasized that despite these mixed signals, causality cannot be inferred from pharmacovigilance data alone

A recent pharmacovigilance analysis by Zhou et al.[347] explored the potential association between GLP-1RA and suicidal or self-injurious behaviors (SSIBs) using the FAERS database from 2018 to 2022. The study identified 204 cases of SSIBs involving GLP-1RA including semaglutide, liraglutide, dulaglutide, exenatide, and albiglutide. Time-to-onset analysis revealed no consistent pattern in latency for these events. Importantly, disproportionality analysis found no significant signal indicating an increased risk of SSIBs with GLP-1RA use. Notably, co-medication with antidepressants, antipsychotics, or benzodiazepines was common among reported cases, suggesting underlying mental health conditions may contribute to the observed events. The authors concluded that there is no evidence of a disproportionate reporting signal linking GLP-

1RA to SSIBs, supporting their relative psychiatric safety; however, they recommended vigilance in patients receiving neuropsychotropic medications.

Wang et al.[348] conducted a retrospective pharmacovigilance study using the FAERS data from 2004 to 2024 to assess the association between glucagon-like peptide-1 receptor agonists (GLP-1RA) and depression or suicide/self-injury events in the context of weight management. The analysis included 8,284 reports for liraglutide, 14,435 for semaglutide, and 15,597 for tirzepatide. Significant signals for both depression (ROR 1.87; 95% CI 1.60–2.20) and suicide/self-injury events (ROR 1.73; 95% CI 1.46–2.04) were observed exclusively for semaglutide, with effects consistent across sexes and most pronounced in individuals aged 18–64 years. Reporting increased notably after weight management approval, particularly in Europe and North America. Notably, tirzepatide demonstrated a significantly lower mortality rate (0.26%) compared to the other GLP-1RA, suggesting a potentially safer profile for patients with psychiatric comorbidities requiring weight reduction. These findings highlight the importance of careful monitoring of psychiatric adverse events with semaglutide.

Pharmacovigilance data suggest possible signals of psychiatric adverse events with some GLP-1RA, notably semaglutide, but these findings are limited by reporting bias and absence of causality assessment. Regulatory agencies including the FDA and EMA have reviewed available evidence and currently conclude there is no confirmed causal link between GLP-1RA and suicidality.

Given the mixed findings from observational studies and pharmacovigilance reports, continued vigilance is warranted, and the apparent discordance between preclinical evidence suggesting

antidepressant effects of GLP-1RA and real-world signals of possible psychiatric harm highlights the need to better understand the underlying neurobiological mechanisms and contextual factors.

1.4.3.2 Evidence from people with HIV

To date, no studies to our knowledge have examined the effects of GLP-1 agonists, particularly semaglutide, on mental health outcomes among PWH, despite the high prevalence of depression in this population. Existing evidence from the general population currently shows mixed findings: some studies suggest potential risks, others indicate benefits, and several report neutral effects. These studies primarily examined incident depression and suicidality, excluding individuals with pre-existing depression. They largely relied on ICD codes, which may under-ascertain cases, and were affected by methodological biases, limiting both the validity of the findings and their applicability to PWH, highlighting the need for population-specific research.

PWH differ from the general population in ways that may influence neuropsychiatric responses, further reinforcing the need for population-specific research. They experience high rates of depression driven by HIV-related stigma, substance use, trauma, psychosocial stressors, chronic inflammation, and ART-related neuropsychiatric side effects.[166] They are also more likely to have metabolic complications such as obesity and diabetes, which further increase the risk of depression and reduce quality of life.[181,182,349] GLP-1RA act on central pathways regulating appetite, mood, and reward, and their neuropsychiatric effects may be altered in PWH due to HIV-related changes in neuroinflammation, neurotransmitter balance, and hypothalamic–pituitary–adrenal (HPA) axis function.[177–180] As GLP-1RA are increasingly used in PWH to manage

obesity and diabetes, understanding these population-specific interactions is critical. There is potential for both beneficial and adverse effects on mood, and the presence of multiple comorbidities and polypharmacy raises additional concerns regarding drug–drug interactions, adherence, and tolerability.

1.5 Rationale and Research Objectives

1.5.1 Rationale

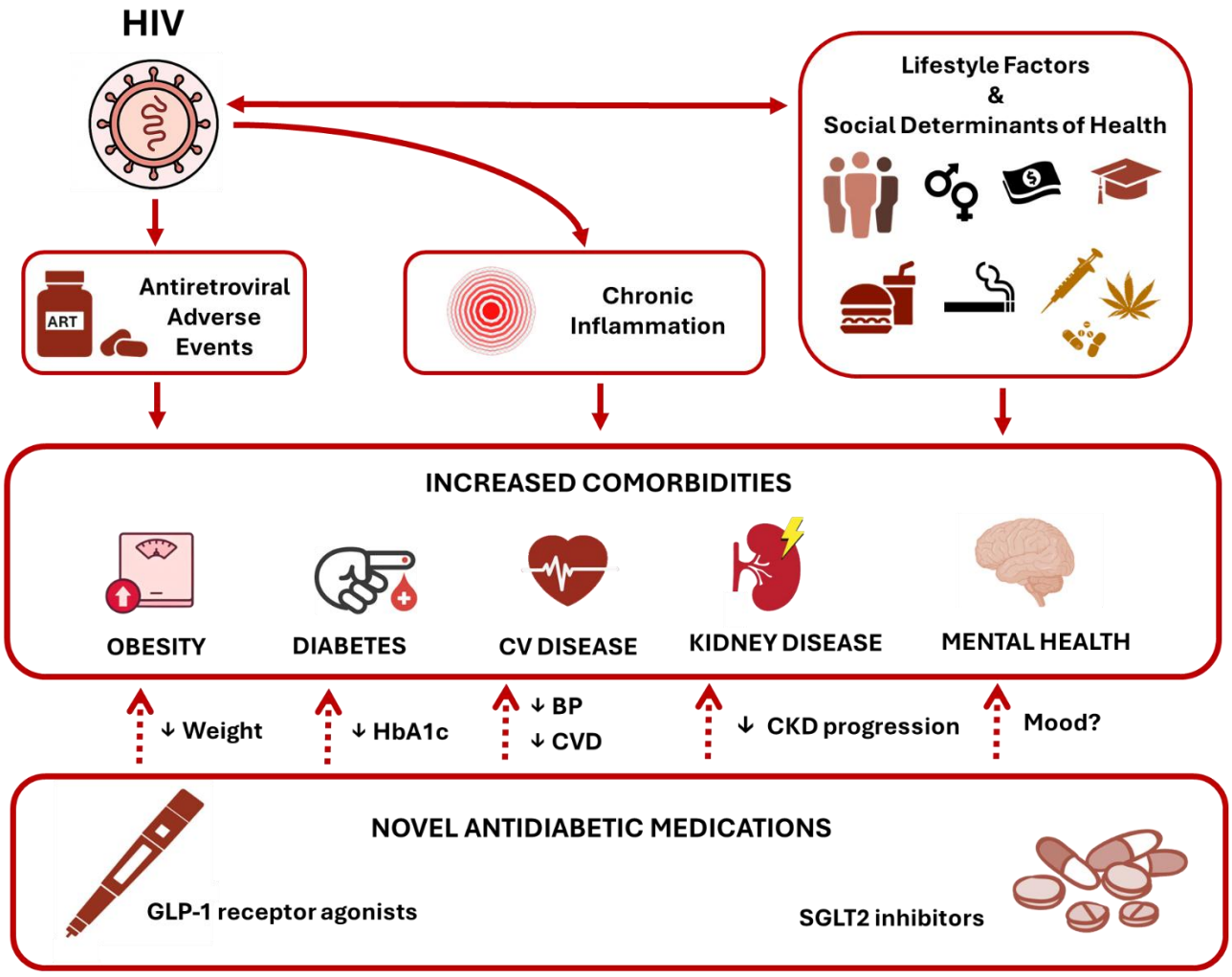
People with HIV (PWH) are living longer due to effective antiretroviral therapy (ART), but face a growing burden of chronic conditions such as type 2 diabetes (T2D), obesity, cardiovascular disease (CVD), chronic kidney disease (CKD), and mental health disorders.[3,6,103] These comorbidities are more prevalent and often emerge earlier among PWH compared to the general population, driven by a complex interplay of HIV-related inflammation, ART exposure, and social determinants of health. As a result, managing metabolic and mental health comorbidities has become an increasingly important component of comprehensive HIV care.

Novel antidiabetic agents, particularly GLP-1RA and SGLT2 inhibitors hold potential in managing diabetes, obesity, and delaying kidney disease progression, offering a promising avenue for addressing unmet needs among PWH. Emerging preclinical evidence also suggests that GLP-1RA may have neuroprotective and antidepressant properties, potentially improving mental health outcomes. However, some clinical reports and pharmacovigilance data have signaled a possible association between GLP-1RA and increased risk of depression and suicidal ideation, raising important safety concerns. For SGLT2 inhibitors, while long-term renal benefits are well-established in the general population, the initial eGFR dip seen after initiation may be concerning in a population already at elevated risk of kidney impairment.

Despite these considerations, randomized controlled trials and real-world evidence on the safety and effectiveness of GLP-1RA and SGLT2 inhibitors among PWH remains limited. Preliminary studies suggest that semaglutide, a GLP-1RA, may result in substantial weight loss in this population, but its mental health effects have not been studied. Similarly, very few studies have examined the impact of SGLT2 inhibitors on diabetes control, weight change or kidney outcomes in PWH. Furthermore, head-to-head comparisons of novel versus older antidiabetic drug classes (e.g., DPP4 inhibitors, sulfonylureas) in this population are lacking. Current prescribing practices rely largely on evidence from the general population, which may not fully apply to PWH given their unique clinical and social vulnerabilities.

PWH face intersecting metabolic, clinical, and social challenges that may modify disease progression and treatment response. In addition to high rates of comorbidities, they often experience social vulnerabilities such as economic marginalization, stigma, mental health disorders, and substance use, which can further complicate access to care, adherence, and health outcomes. Figure 1.1 illustrates these pathways and the potential roles of GLP-1RAs and SGLT2 inhibitors in PWH. Moreover, GLP-1RA and SGLT2 inhibitors are substantially more expensive than older agents, and PWH disproportionately experience economic marginalization, highlighting the importance of population-specific evidence and contextual evidence. Generating such evidence is critical to inform clinical decision-making, guide guideline development, support patient-centered care, and optimize the use of novel antidiabetic therapies in PWH. Such evidence can ultimately improve health outcomes and ensure the optimal, safe, and equitable use of novel antidiabetic therapies in this population.

Figure 1.1. HIV-Related Mechanisms Driving Comorbidities and the Potential Role of Novel Antidiabetic Medications



This figure illustrates the multifactorial pathways contributing to the elevated burden of cardiometabolic and mental health comorbidities among people with HIV (PWH). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors may offer metabolic, cardiovascular, and renal benefits. Dashed arrows indicate hypothesized benefits in PWH, reflecting the limited evidence base in this population.

1.5.2 Thesis Objectives

The overall aim of this thesis is to evaluate the safety and effectiveness of novel antidiabetic medications among PWH, with a focus on clinically important outcomes including weight change, kidney function, and depressive symptoms. Specific objectives include:

- **Objective 1**: To evaluate the impact of antidiabetic medications on bodyweight and glycemic control among PWH. This includes two complementary studies:
    - A real-world study assessing change in bodyweight and hemoglobin A1c (HbA1c) among semaglutide new users (Chapter 2).
    - A comparative effectiveness study evaluating changes in bodyweight and HbA1c among new users of GLP-1RA, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas (Chapter 3).
    - **Hypothesis**: GLP-1RA, particularly semaglutide, will be associated with the greatest weight reduction, followed by SGLT2 inhibitors. DPP-4 inhibitors are expected to have a neutral effect on weight, while sulfonylureas will likely be associated with weight gain.
- **Objective 2**: To assess the impact of SGLT2 inhibitors on kidney function among PWH, in comparison to other antidiabetic medications, by evaluating both acute changes in estimated glomerular filtration rate (eGFR) following initiation and longer-term eGFR trajectories (Chapter 4).

- **Hypothesis**: SGLT2i use will be associated with a modest acute eGFR decline, followed by slower long-term decline in kidney function compared to other antidiabetic classes.

- **Objective 3:** To examine the effect of semaglutide on depressive symptoms among PWH (Chapter 5).
  - **Hypothesis**: Given preclinical evidence suggesting potential antidepressant effects, mixed findings in the general population, and the unique characteristics of PWH, clinical equipoise exists, and semaglutide use may be associated with improvement, no change, or worsening of depressive symptoms in this population.

Chapter 2. Weight Loss Associated with Semaglutide Treatment Among People with HIV

2.1 Overview

This chapter presents the first manuscript addressing Objective 1, evaluating the impact of semaglutide on bodyweight and glycemic control among people with HIV (PWH). Although semaglutide has proven effective for weight loss and glycemic control in the general population; PWH, who have disproportionately high rates of obesity and diabetes, have been largely excluded from clinical trials.

Using data from CNICS, a large multicenter U.S. cohort, we included PWH who newly initiated semaglutide between 2018 and 2022. Adjusted linear mixed models were used to evaluate changes in body weight and glycemic control at one year. We found that semaglutide was associated with meaningful weight loss and improved glycemic control, consistent with findings in the general population. These findings support semaglutide as a promising option for managing obesity and diabetes among PWH.

Manuscript status: Published

Citation: Haidar L, Crane HM, Nance RM, et al. Weight loss associated with semaglutide treatment among people with HIV. *AIDS*. 2024;38(4):531-535. doi:10.1097/QAD.0000000000003791

Weight Loss Associated with Semaglutide Treatment Among People with HIV

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2.2 Abstract

Objective There is limited real-world evidence about the effectiveness of semaglutide for weight loss among people with HIV (PWH). We aimed to investigate weight change in a US cohort of PWH who initiated semaglutide treatment.

Design Observational study using the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.

Methods We identified adult PWH who initiated semaglutide between 2018 and 2022 and with ≥2 weight measurements. The primary outcome was within-person bodyweight change in kg at 1 year. The secondary outcome was within-person Hemoglobin A1c percent (HbA1c) change. Both outcomes were estimated using multivariable linear mixed model.

Results In total, 222 new users of semaglutide met inclusion criteria. Mean follow up was 1.1 years. Approximately 75% of new semaglutide users were male, and at baseline, mean age was 53 years (standard deviation [SD]: 10), average weight was 108 kg (SD: 23), mean body mass index was 35.5 kg/m^2, mean HbA1c was 7.7% and 77% had clinically recognized diabetes. At baseline, 97% were on ART and 89% were virally suppressed (VL< 50 copies/mL). In the adjusted mixed model analysis, treatment with semaglutide was associated with an average weight loss of 6.47 kg at 1 year (95% CI -7.67 to -5.18) and with a reduction in HbA1c of 1.07% at 1 year (95% CI -1.64 to -0.50) among the 157 PWH with a post-index HbA1c value.

Conclusions Semaglutide was associated with significant weight loss and HbA1c reduction among PWH, comparable to results of previous studies from the general population.

2.3 Introduction

Advancements in and early initiation of antiretroviral therapy (ART) have resulted in the reduction of HIV-associated wasting among people with HIV (PWH). In contrast, there has been an increase in weight gain and obesity, mirroring the obesity epidemic seen in the general population (1,2). This weight gain has been attributed to dietary and other lifestyle factors, living to older ages due to advances in ART, and direct and indirect effects of ART (2). The indirect effect of ART on weight is through suppression of the viral load and return to a normal metabolic state. Direct effects are due to impact of some classes of ART which are more likely to cause weight gain and metabolic side effects (3). Integrase strand transfer inhibitors (INSTIs), especially dolutegravir and bictegravir, are associated with the most weight gain (4). If untreated, obesity can ultimately lead to multiple metabolic and cardiovascular complications, including Type 2 Diabetes (T2D). PWH are already at a higher risk of these complications(5), and obesity further increases their risk. Therefore, it is imperative to treat weight gain in this population.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for the treatment of T2D, and more recently for obesity at higher doses for patients with a BMI ≥30 kg/m^2 or a BMI≥27 kg/m^2 and at least one comorbidity (6). It is available as either an injectable administered subcutaneously (SQ) once weekly or oral tablets administered once daily. Randomized controlled trials (RCTs) in the general population have reported significant and sustained weight loss with semaglutide among both those with and without diabetes (7–13). However, among PWH there is limited real-world evidence about the effectiveness of semaglutide for weight loss. We aimed to investigate weight change in a US cohort of PWH who initiated semaglutide treatment.

2.4 Methods

We conducted an observational within-person longitudinal study in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort. The CNICS cohort is a dynamic, prospective, clinical cohort of PWH aged 18 and older in care at ten academic sites across the United States. This study included data from eight CNICS sites: University of Alabama at Birmingham, Case Western Reserve University, University of Washington, University of California San Diego, Fenway Health/Harvard University, University of North Carolina Chapel Hill, Johns Hopkins University, and Vanderbilt University. All participants completed informed consent prior to entry into CNICS.

We identified adult PWH who initiated injectable or oral semaglutide in HIV care between 2018 and 2022. Date of first prescription of semaglutide was considered the index date or baseline. PWH were included if they had no previous record of semaglutide use, and at least 2 weight measurements: bodyweight at index date, defined as the most recent bodyweight measurement within one year prior to the index date, and at least one post-index weight measurement occurring at any time after initial prescription date. For those with more than one post-index weight, the last recorded measurement while on semaglutide treatment was used to calculate bodyweight change. Bodyweight change was calculated as post-index bodyweight minus bodyweight at the index date. Follow up ended at the last recorded weight before semaglutide discontinuation.

The primary outcomes of interest were the trajectory of within-person bodyweight change in kg and percentage of bodyweight change at 1 year. The secondary outcome was the trajectory of within-person Hemoglobin A1c (HbA1c) percent change at 1 year. We excluded participants from

the secondary outcome who did not have HbA1c values prior to and after treatment initiation. The primary and secondary outcomes were estimated using a linear mixed model with a random intercept and a random slope using exchangeable covariance matrix to account for repeated measures on participants. Models were adjusted for age, sex, race/ethnicity, CNICS site, diabetes status as a binary variable, CD4 cell count, HIV viral load (VL), and a non-linear time term ($time^2$). Covariate definitions have been previously defined (4). We assumed that all PWH who received a semaglutide prescription took the medication, as it was not possible to directly evaluate medication adherence. We also investigated whether the effect of semaglutide on weight change differed based on the administration of INSTI. Analyses were conducted using Stata version 17 (StataCorp, College Station, TX).

2.5 Results

In total, 222 new users of semaglutide were identified in the CNICS cohort in the relevant time period. Mean follow up was 1.1 years. Approximately 75% of new semaglutide users were male, mean age at baseline was 53 years (standard deviation [SD]: 10), average baseline weight was 108 kg (SD: 23), and mean body mass index (BMI) was 35.5 kg/m^2. Mean hemoglobin A1c (HbA1c) was 7.7% and 77% had clinically recognized diabetes at baseline. At semaglutide initiation, 54% were on metformin, 39% were on insulin, and 15% were on a Sodium-glucose Cotransporter-2 (SGLT2) Inhibitor. At baseline, 89% were virally suppressed (VL < 50 copies/mL) and 97% were on ART, with 82% receiving an INSTI based regimen. In addition, 18% were on a concomitant antipsychotic medication at baseline (Table 2.1).

Of the 125 patients who had available data on the maximum dose reached, 87 (69.6%) received low doses of subcutaneously injected semaglutide (0.25, 0.5, and 1 mg), while 24 (19.2%)

received high doses of subcutaneously injected semaglutide (1.7, 2, and 2.4 mg). The remaining 14 (11.2%) were on oral doses of 3, 7, or 14 mg.

In fully adjusted mixed models, treatment with semaglutide was associated with significant bodyweight loss: 6.47 kg at 1 year (95% CI: -7.71 to -5.23) (Figure 2.1) and percent bodyweight loss: 5.72% (-6.86 to -4.58) at 1 year among 222 PWH. Reductions in body weight were -6.49 (-7.77, -5.21) kg ($p < 0.001$) in people receiving INSTI and -6.38 (-8.10, -4.66) kg ($p < 0.001$) in people not receiving INSTI. There was no significant difference between the two groups (p for interaction =0.883), verifying that PWH receiving an INSTI lost weight. In addition, treatment with semaglutide was also associated with a significant reduction in HbA1c: 1.07% at 1 year (95%CI -1.64 to -0.50) among the 157 PWH with a post-index HbA1c value.

2.6 Discussion

Among PWH in our cohort who were new users of semaglutide, a significant weight loss of 6.47 kg was observed at 1 year. Our results are consistent with the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) and Semaglutide Treatment Effect in People with Obesity (STEP) randomized controlled trials, which included people without HIV with diabetes and/or obesity. The average weight loss achieved in STEP-2 in patients with T2D and obesity (mean BMI 35.7 kg/m^2) after 68 weeks of treatment using the 1 mg semaglutide SQ once weekly dose was -6.90 kg, which was comparable to our study (-6.47 kg) (14). A 1.5% reduction in HbA1c was observed in STEP-2 with 1 mg semaglutide. The weight loss achieved by the 0.5 and 1 mg SQ doses in the SUSTAIN 1 through 11 trials ranged from -3.5 to -6.5 kg (7–13); the higher end of this range being similar to the weight loss achieved in our study.

Previous real-world evidence from the general population is also consistent with our findings. A post hoc analysis of four Semaglutide Real-world Evidence (SURE) studies (SURE Canada, Denmark/Sweden, Switzerland and UK) including 1,212 patients with T2D and a mean BMI of 35 kg/m^2 treated with lower doses of SQ semaglutide for approximately 30 weeks (52 weeks permissible in UK study), showed a significant decrease of body weight of 4.7 kg, slightly less weight loss compared with our study likely due to shorter follow-up time in the SURE studies (15). HbA1c reductions observed in our study were also consistent with the SURE studies. Reductions in weight were less pronounced in our study compared to a retrospective study including 175 patients assessing weight loss among people who were overweight or obese, where patients lost an average weight of 12.3 (6.6) kg after 6 months; this could be due to 44% of patients taking higher doses of semaglutide (1.7 or 2.4 mg) (6). Furthermore, only 16% of patients had diabetes and generally patients with T2D experience less dramatic weight loss compared to those without diabetes.

This study expands on findings from general population studies with respect to semaglutide as a weight loss agent by focusing on PWH. Despite the metabolic effects of ART, our results provide evidence that semaglutide, even at lower doses, is an effective treatment option for weight loss and diabetes control among PWH. Semaglutide has also been shown to reduce the risk of cardiovascular disease and chronic kidney disease among people with T2D (7). Semaglutide might be especially beneficial for PWH with other comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and early-stage chronic kidney disease, however future studies among PWH are warranted to confirm these benefits given the complex dynamics of HIV- disease and other comorbidities.

There are a number of important strengths and limitations to this study. The CNICS cohort is a prospective, longitudinal, and dynamic cohort, enabling the capture of PWH in routine clinical care. Unlike RCTs, it does not have eligibility restrictions, making its findings generalizable to geographically and demographically diverse PWH in care. Our cohort of new semaglutide users among PWH offers a heterogeneous, real-world assessment that demonstrates clinically relevant levels of weight loss after one year of treatment. While we do not emulate a clinical trial specifically, we used a quasi-experimental approach, which eliminates the impact of potential within-person confounding factors. Limitations include the inability to account for adherence, the risk of time-varying confounding from an unknown factor given the observational nature of this study, some participants may have been censored before their first post-index weight measurement, missing HbA1c values, and missing prescribed semaglutide doses in some patients. Furthermore, due to the small sample size and missing dose data in certain sites, the study was underpowered for conducting subgroup analyses by dose and route of administration. Moreover, the COVID-19 pandemic resulted in a decrease in recorded weight measurements in the clinic, which could have introduced a bias towards the null. Although the average follow-up time was around 1 year, studies with longer follow-up time are warranted to assess the durability of semaglutide in achieving weight loss and improving HbA1c among PWH.

2.7 Conclusion

This study is an important step forward, showing that semaglutide significantly decreases bodyweight and HbA1c among PWH and thus, may play a key role in the obesity and diabetes epidemics in this population. Despite the lower range of semaglutide doses used, semaglutide

demonstrated significant benefit in PWH both in terms of weight loss and diabetic control. Future work is needed to find optimal treatment and dosing recommendations for this important high-risk population.

2.8 Tables and Figures

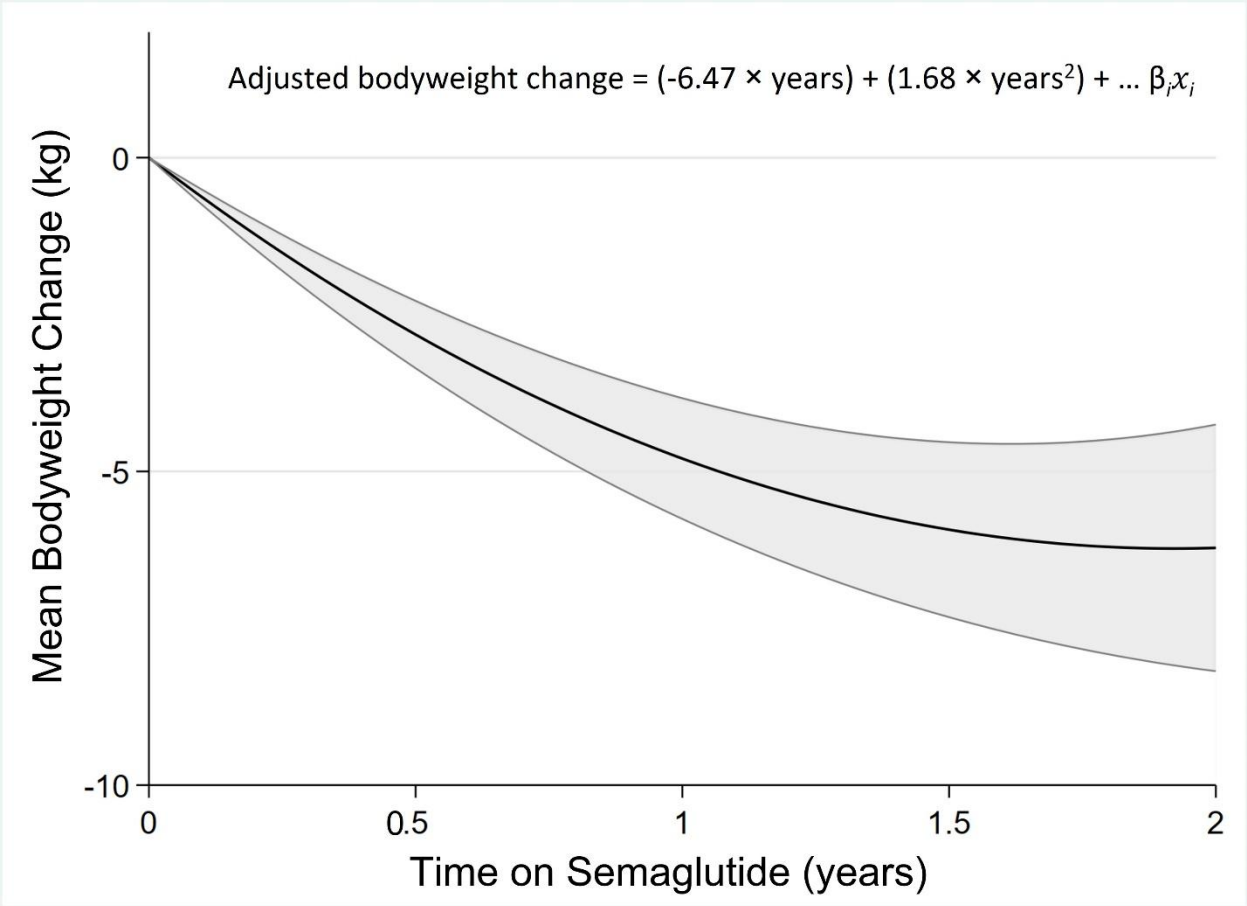
Table 2.1. Baseline characteristics for people with HIV initiating treatment with semaglutide

Variable	Mean (SD) or n (%)
N	222
Age (years)	52.8 (10.2)
Males	166 (74.8)
Race/ethnicity	
White	107 (48.2)
Black	78 (35.1)
Hispanic	33 (14.9)
Other/missing	4 (1.8)
HbA1c % (n=219)	7.7 (2.2)
Diabetes	170 (76.6)
Treated Hypertension	167 (75.22)
Weight (kg)	107.6 (23.0)
BMI[a] (kg/m^2)	35.5 (7.0)
BMI categories	
Normal (18.5 – 24.9 kg/m^2)	11 (4.9)
Overweight (25.0 – 29.9 kg/m^2)	36 (16.2)
Obesity Class I (30.0 – 34.9 kg/m^2)	65 (29.3)
Obesity Class II (35.0 – 39.9 kg/m^2)	60 (27.0)
Obesity Class III (≥ 40.0 kg/m^2)	50 (22.5)
CD4 cell count (n=220)	796 (392)
HIV VL <50 copies/mL	198 (89.2)
ART	216 (97.3)
Integrase inhibitor	183 (82.4)
TAF	154 (69.37)
Metformin	121 (54.5)
Insulin	86 (38.7)
Antipsychotic	40 (18.0)
SGLT-2 inhibitor	34 (15.3)
Lipoatrophy score (n=125)	
None (0)	94 (75.2)
Mild (1-12)	31 (24.8)
Moderate-Severe (>12)	0 (0.0)
Lipohypertrophy score (n=125)	
None (0)	38 (30.4)
Mild (1-12)	72 (57.6)
Moderate-Severe (>12)	15 (12.0)
ASCVD[b] risk score (n=219)	
Low risk <5%	47 (21.46)
Borderline 5-<7.5%	19 (8.68)
Intermediate 7.5- <20%	73 (33.33)
High risk ≥ 20	80 (36.53)

Abbreviations: BMI, Body Mass Index; VL, Viral Load; ART, Antiretroviral Therapy; TAF, Tenofovir Alafenamide; SGLT-2, Sodium-Glucose Transport Protein 2 Inhibitor; ASCVD, Atherosclerotic Cardiovascular Disease

[a]BMI is calculated as weight in kilograms divided by height in meters squared.
[b]ASCVD risk score is a 10-Year risk calculator to predict the risk of a first atherosclerotic cardiovascular event.

Figure 2.1. Adjusted bodyweight change (and 95% CI) over time among people with HIV who are new users of semaglutide. Linear mixed regression model of adjusted bodyweight as a dependent variable. For each additional year, bodyweight is expected to decrease by 6.47 kg.



2.9 Contributions of Authors:

Study and analytic design: L.H., R.M.N., H.M.C, S.A.R, L.N.D., B.MW., S.E, and J.A.C.D. **Statistical analysis:** L.H., R.M.N. **Manuscript writing and revising:** L.H., H.M.C., R.M.N., A.W., S.A.R., B.M.W., A.L.W., S.N., L.S.M., C.L., A.L., L.A., M.D., A.H., M.S.S., L.B., E.C., M.M.K, K.H.M., J.J., R.D.M, J.A.C.D., L.N.D., S.E.

All authors gave meaningful input on the manuscript. All authors have approved the final article.

Acknowledgments: The authors would like to acknowledge all CNICS study participants and personnel for their contributions to this work.

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2.11 Additional Results (Not Included in the Submitted Manuscript)

In addition to the results reported in the manuscript chapter above, we conducted additional analyses to examine whether the effect of semaglutide on weight change differed by baseline body mass index (BMI) category, semaglutide dose, and diabetes status. These stratified analyses were not included in the published manuscript as the study was not powered to detect subgroup differences; however, they are presented here to provide further context.

2.11.1 Effect Modification by BMI Category

Weight loss was evaluated across five baseline BMI categories (Additional Table 2.1). A trend toward greater weight loss with increasing BMI was observed, with individuals in Obesity Class III (BMI ≥ 40 kg/m²) experiencing the largest reductions in body weight (−8.8 kg; 95% CI: −10.9, −6.7). Weight loss was significantly greater in this group compared to those with normal weight, overweight, and Obesity Class I BMI (*p* for interaction < 0.05).

Additional Table 2.1. Weight loss results stratified by BMI class

BMI Class	n (%)	Weight Loss, kg (95% CI)
Normal (18.5–24.9 kg/m²)	11 (4.9)	−4.1 (−7.9, −0.2)
Overweight (25.0–29.9 kg/m²)	36 (16.2)	−4.6 (−6.9, −2.3)
Obesity Class I (30.0–34.9 kg/m²)	65 (29.3)	−5.4 (−7.3, −3.4)
Obesity Class II (35.0–39.9 kg/m²)	60 (27.0)	−7.6 (−9.5, −5.7)
Obesity Class III (≥40.0 kg/m²)	50 (22.5)	−8.8 (−10.9, −6.7)

2.11.2 Effect by Semaglutide Dose

We also stratified the analysis by semaglutide dose (low vs. high). Both groups experienced significant weight reductions (Additional Table 2.2), with greater losses observed in the high-dose group (−12.1 kg; 95% CI: −17.5, −6.6) compared to the low-dose group (−9.0 kg; 95% CI: −10.8, −7.1). However, the difference in effect was not statistically significant (*p*-value for interaction = 0.27).

Additional Table 2. 2. Weight loss results stratified by semaglutide dose (N=125)

	Low Dose	**High Dose**
Weight change (95% CI)	-9.0 kg (-10.8, -7.1)	-12.1 kg (-17.5, -6.6)
P-value	<0.001	<0.001
	p for interaction: 0.27	

2.11.3 Effect by Diabetes Status

Lastly, we explored whether diabetes status modified the effect of semaglutide. As shown in Additional Table 2.3, non-diabetic individuals lost more weight (−8.6 kg; 95% CI: −11.5, −5.7) than those with diabetes (−6.2 kg; 95% CI: −7.8, −4.9). This difference did not reach statistical significance (*p*-value for interaction = 0.12).

Additional Table 2.3. Weight loss results stratified by diabetes status

	Diabetic	**Non-diabetic**
Weight change (95% CI)	-6.2 kg (-7.8, -4.9)	-8.6 kg (-11.5, -5.7)
P-value	<0.001	<0.001
	p for interaction: 0.12	

Chapter 3. Comparative Effectiveness of GLP-1RAs, SGLT2 Inhibitors, DPP-4 Inhibitors, and Sulfonylureas on Weight Change in People with HIV: A Real-World Longitudinal Cohort Study

3.1 Overview

This manuscript is the second manuscript addressing the weight-related aim (objective 1) of this thesis, expanding beyond the single-drug semaglutide study to compare four antidiabetic drug classes: GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas on weight change among people with HIV (PWH).

Using an active comparator new user cohort of 1,572 PWH, GLP-1RA users experienced the greatest and clinically meaningful weight loss at one year (–4.44%; 95% CI: –5.51 to –3.36), especially among those without diabetes, with higher baseline BMI, and receiving semaglutide. SGLT2 inhibitors offered modest weight loss benefits primarily in people with diabetes. DPP-4 inhibitors and sulfonylureas had minimal impact on weight. For PWH needing focused weight management, GLP-1 receptor agonists are the preferred option.

Manuscript status: Manuscript under review

Comparative Effectiveness of GLP-1 Receptor Agonists, SGLT2 Inhibitors, DPP-4 Inhibitors, and Sulfonylureas on Weight Change Among People with HIV: A Real-World Longitudinal Cohort Study

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3.2 Abstract

Background

People with HIV (PWH) are at elevated risk of obesity, yet evidence on weight loss with newer antidiabetic medications in this population remains limited. We compared the effects of glucagon-like peptide 1 receptor agonists (GLP-1RA), sodium–glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidase 4 inhibitors (DPP-4i), and sulfonylureas on bodyweight change among PWH.

Methods

We conducted an active-comparator new-user cohort study using data from 9 U.S. sites in the Centers for AIDS Research Network of Integrated Clinical Systems. PWH initiating GLP-1RA, SGLT2 inhibitors, DPP-4i, or sulfonylureas between 2013 and 2023 were included. The primary outcome was percent bodyweight change at 1 year, assessed using covariate-adjusted linear mixed models under an on-treatment approach. Secondary outcomes included absolute weight change (kg) and time to ≥5% and ≥10% loss, evaluated using adjusted Cox models. Additionally, weight change trajectories up to 3 years were examined for nonlinear patterns.

Results

Among 1,572 PWH, GLP-1RA users had the greatest mean percent weight loss at 1 year (–4.44%; 95% CI –5.51 to –3.36), followed by SGLT2 inhibitors (–1.00%; 95% CI –2.25 to 0.24). DPP-4i and sulfonylureas showed minimal change. Compared to sulfonylureas, GLP-1RA and SGLT2 inhibitor users were significantly more likely to achieve clinically meaningful weight loss ≥5% and ≥10%. Weight loss with GLP-1RA was greater among PWH without diabetes and those with higher body mass index, with semaglutide achieving the largest reductions. Additional analyses suggested

that GLP-1RA–associated weight loss was nonlinear, with rapid early reductions followed by slower declines.

Conclusions

GLP-1RA led to the greatest weight loss among PWH, supporting their use in a population with high cardiometabolic risk.

3.3 Introduction

Following the widespread adoption of antiretroviral therapy (ART), life expectancy among people with HIV (PWH) has approached that of the general population.[1] However, new challenges have emerged, including a rising prevalence of obesity among PWH.[2,3] Weight gain in PWH often exceeds what would be expected from "return-to-health" alone and reflects both the obesogenic environment and HIV-specific factors such as chronic inflammation, immune activation, and certain first-line ART regimens.[2–6] Integrase strand transfer inhibitors (INSTIs) like dolutegravir and bictegravir, and the nucleoside reverse transcriptase inhibitor tenofovir alafenamide (TAF), have been implicated in ART-associated weight gain.[7–10] Rising obesity rates among PWH may increase the risk of type 2 diabetes, cardiometabolic disease, and reduce overall quality of life making effective weight management essential in modern HIV care.[11–14] As ART prolongs life expectancy among PWH, managing these complications appropriately has the potential to further improve these gains. Consequently, addressing obesity and its metabolic consequences has become a critical component of comprehensive HIV care.

Novel antidiabetic medications, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, have transformed the management of type 2 diabetes. Select GLP-1RAs, including semaglutide, liraglutide, and the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide, are also approved for obesity and induce clinically meaningful weight loss. Both GLP-1RAs and SGLT2 inhibitors improve glycemic control and confer cardiovascular and renal benefits.[15–18] Other commonly used antidiabetic medication classes such as dipeptidyl peptidase-4 (DPP-4 inhibitors) inhibitors and sulfonylureas

lack these broader health benefits and are weight neutral or may contribute to weight gain, respectively.[19]

Although small studies, particularly those involving semaglutide, suggest that GLP-1RA are effective for weight management in PWH,[20–22] evidence regarding the effectiveness of GLP-1RA and SGLT2 inhibitors remains limited. Moreover, comparisons of weight outcomes between these newer agents and older antidiabetic drug classes in this population are lacking. This study evaluates weight change following initiation of GLP-1RA, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas among PWH receiving care in the United States.

3.4 Methods

3.4.1 Data source

We examined participants in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, an ongoing multicenter observational cohort of over 50,000 adults with HIV receiving care across 10 sites in the United States.[23] For this analysis, data from nine participating sites were included. Each site obtained approval from its local institutional review board for participation in CNICS.

3.4.2 Study design and population

We conducted an active comparator, new-user cohort study of PWH who initiated treatment with medications from one of four antidiabetic classes, GLP-1RA, SGLT2 inhibitors, DPP-4 inhibitors, or sulfonylureas, between 2013 and 2023. Medication exposure data in CNICS were obtained from electronic medical records including provider order entry and/or pharmacy dispensing systems. Exposure was defined by the presence of at least one prescription record. New users were defined as individuals with no prior exposure to any of the four study antidiabetic classes. Active

comparators were chosen to reduce confounding by indication from comparing users to non-users. Each participant was assigned exclusively to one exposure group based on their first exposure and could not have previously received medications from any of the other classes. The date of antidiabetic medication initiation was designated as the index date. A detailed list of included medications by class is provided in Supplemental Table 3.1.

The study included PWH with at least one weight measurement within the one year prior to medication initiation, with the measurement closest to treatment initiation characterized as the baseline weight, and at least one weight measurement within one year after initiation characterized as the follow-up weight. PWH who initiated two or more antidiabetic classes on the index date were excluded to ensure that observed outcomes could be attributed to a single medication class. Participants were followed from the index date until the earliest of medication discontinuation or switch, occurrence of the outcome (for time-to-event analyses), end of available clinical data, or a maximum of one year.

3.4.3 Outcomes

The primary outcome was the percentage change in bodyweight at one year, calculated as: ((follow-up weight − baseline weight) / baseline weight) × 100. Weight measurements were recorded as part of routine care at outpatient visits. Secondary outcomes included: (1) absolute weight change in kg from baseline to one year; (2) time to achieving clinically meaningful weight reduction, defined as ≥5% and ≥10% decrease from baseline bodyweight. Primary and secondary outcomes were assessed using all weight measurements recorded within 1 year of medication initiation. For all outcomes, GLP-1RA, SGLT2 inhibitors, and DPP-4 inhibitors were compared to

sulfonylureas, which served as the reference group given their long-standing and common use as second-line agents.

In addition to the primary 1-year outcome, we explored longer-term and possible non-linear trends in percentage weight change using piecewise linear spline models incorporating all available weight measurements up to 3 years after medication initiation among all participants who had measurements beyond 1 year.

3.4.4 Covariates

We examined potential confounders and baseline risk factors, measured at or prior to medication initiation, including demographics (age, sex, CNICS site, race/ethnicity [non-Hispanic White, non-Hispanic Black, Hispanic, Other]); clinical factors including HIV-specific variables (CD4 count, HIV viral load, ART use), comorbidities (hypertension, type 2 diabetes), estimated glomerular filtration rate (eGFR), medication use (metformin, insulin, statins, antipsychotics), and smoking history (ever vs. never). Based on CNICS operational definitions, type 2 diabetes was defined as having one of the following: hemoglobin A1c ≥6.5%, use of diabetes-specific medication (e.g., insulin, sulfonylureas), or use of diabetes-related medication (e.g., metformin) with a diabetes diagnosis.[24] Hypertension was defined as the presence of both a diagnosis and treatment with antihypertensive medications. eGFR was calculated using the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[25]

3.4.5 Statistical analyses

Primary and secondary outcomes

The primary outcome, percentage weight change at 1 year, was analyzed using linear mixed models (LMMs) with random intercepts and random slopes for time. The random intercepts

captured differences in baseline weight across participants, while the random slopes accounted for individual variation in weight change over time. Antidiabetic medication class was included as a fixed effect to compare weight change across the four groups, with an interaction term between time and treatment group to allow weight trajectories to differ by medication class. LMMs account for repeated measurements within participants and leverage all available weight measurements through follow-up, accommodating varying numbers and timing of observations per participant. This approach ensures that every follow-up weight contributes to the analysis, rather than relying on a single post-initiation measurement. To mitigate confounding, models were adjusted for baseline demographic factors (age, sex, race/ethnicity, CNICS site), clinical characteristics (hypertension, diabetes, eGFR, weight, CD4 cell count, HIV viral load [log10], and cigarette smoking), and use of medications including ART, antipsychotics, statins, insulin, and metformin. We also examined absolute weight change using LMMs, adjusting for the same set of covariates.

Time-to-event outcomes for achieving ≥5% and ≥10% reduction in bodyweight were conducted using multivariable Cox proportional hazards models, adjusted for above baseline covariates. We report adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). In addition, we used Kaplan-Meier models to estimate the cumulative incidence of achieving ≥5% and ≥10% weight loss at 1 year.

Analyses of primary and secondary outcomes estimated on-treatment effects by following PWH from the index date until the earliest of medication discontinuation or switch, outcome occurrence (for time-to-event analyses), end of clinical data, or a maximum of 1 year. Weight

measurements were included only during the period in which participants were prescribed the medication to approximate treatment-related weight change (Supplemental Figure 3.1).

Subgroup and sensitivity analyses

We conducted subgroup analyses to assess whether associations between GLP-1RA or SGLT2 inhibitor use and percent weight change varied by age (≥55 vs. <55 years), sex (male vs. female), baseline diabetes status (yes vs. no), and BMI categories (≥35 and 30-34.9 vs. <30 kg/m^2). We examined PWH on GLP-1RA and SGLT2 inhibitors as these two medication classes have demonstrated significant effects on weight loss. We used Interaction terms between treatment and subgroup to test for effect modification. Within the GLP-1RA group, we also conducted a subgroup analysis to evaluate percentage weight change at one year by specific agents: semaglutide, dulaglutide, liraglutide, and other GLP-1RA agents, adjusting for the same baseline covariates as in the main analysis.

We conducted two sensitivity analyses for the primary outcome: (1) restricting to PWH with type 2 diabetes to reduce confounding by indication, given that GLP-1RA are often prescribed for weight loss in people without diabetes and SGLT2 inhibitors may be used for chronic kidney disease or heart failure, whereas DPP-4 inhibitors and sulfonylureas are typically prescribed solely for diabetes; and (2) an intention-to-treat (ITT) analysis including all follow-up data up to one year, regardless of treatment changes.

Additional analyses: Long-term weight change

To examine trends in percent weight change beyond 1 year and explore potential nonlinearity in weight change over time, we used piecewise linear spline mixed models incorporating all

available follow-up weight measurements up to 3 years, with knots at 6 and 12 months to allow linear slopes to vary across intervals 0–6 months, 6–12 months, and >12 months. These models allowed for a flexible characterization of weight change patterns over time. These models were adjusted for the same baseline covariates as the primary analysis. Not all PWH had weight measurements beyond 1 year; therefore, estimates for later follow-up periods are based on fewer observations.

3.5 Results

3.5.1 Study population and baseline characteristics

Among 1,572 PWH included in this study, 619 initiated GLP-1RA, 290 initiated SGLT2 inhibitors, 199 initiated DPP-4 inhibitors, and 464 initiated sulfonylureas (Supplemental Figure S2). Among GLP-1RA users, 338 (55%) received semaglutide, 165 (27%) dulaglutide, 90 (15%) liraglutide, and 26 (4%) other agents. Overall, the mean age was 53 years (standard deviation [SD]:10), 25% were female, and 46% were Black (Table 3.1). Baseline characteristics differed by group: GLP-1RA users were generally younger and had higher baseline BMI. All DPP-4 inhibitor and sulfonylurea users had type 2 diabetes, whereas a subset of GLP-1RA and SGLT2 inhibitor users did not. SGLT2 inhibitors and DPP-4 inhibitors users had lower baseline eGFR. Over 95% of the cohort was on ART, with the majority having undetectable viral load. Across the study population, a total of 7,275 weight measurements were included in the analysis (GLP-1RA: 2,604; SGLT2 inhibitors: 1,519; DPP-4 inhibitors: 917; sulfonylureas: 2,235). Within the 1-year follow-up period, the median (IQR) number of post-initiation weight measurements per participant was 3 (1–6) for GLP-1RA, 2 (1–5) for SGLT2 inhibitors, and 3 (1–5) for both DPP-4 inhibitors and sulfonylurea users. Overall, 242 (15.4%) participants contributed only one post-initiation weight measurement, with 113/619

(18.2%) in the GLP-1RA group, 35/290 (12.1%) in the SGLT2 inhibitor group, 34/199 (17.1%) in the DPP-4 inhibitor group, and 60/464 (12.9%) in the sulfonylurea group. The median (IQR) maximum follow-up time was 195 (91–308) days for GLP-1RA, 221 (119–318) days for SGLT2 inhibitors, 275 (151–336) days for DPP-4 inhibitors, and 238 (120–317) days for sulfonylurea users.

3.5.2 Primary outcome: Percent weight change at 1 year

In adjusted models, on-treatment weight change at 1 year was greatest among GLP-1RA users, with a mean percent reduction of –4.44% (95% CI: –5.51 to –3.36; Table 3.2 & Figure 3.1A). Use of SGLT2 inhibitors showed a modest, non-significant reduction of –1.00% (95% CI: –2.25 to 0.24), while DPP-4 inhibitors showed minimal change (–0.21%, 95% CI: –1.68 to 1.27). In contrast, sulfonylurea users had a non-significant weight gain of 0.96% (95% CI: –0.05 to 1.97). Compared to sulfonylureas, weight reductions were significantly greater with GLP-1RA and SGLT2 inhibitors ($p < 0.05$), but not with DPP-4 inhibitors.

3.5.3 Secondary outcomes: Absolute weight change and weight loss thresholds

Weight change in kilograms reflected the patterns observed in percentage weight (Table 3.2 & Figure 3.1B). GLP-1RA led to the greatest weight loss (–5.00 kg; 95% CI: –6.19 to –3.81), followed by SGLT2 inhibitors (–1.31 kg; 95% CI: –2.46 to –0.16). DPP-4 inhibitors and sulfonylureas showed minimal, non-significant changes in weight.

At 1 year, GLP-1RA had the highest probability of achieving ≥5% (49.7%) and ≥10% (26.4%) weight loss, followed by SGLT2 inhibitors (41.5% and 21.5%, respectively; Table 3.2). These results are illustrated in Figures 3.1C–D, showing the proportions achieving ≥5% and ≥10% weight loss at 1 year, and in Supplemental Figure 3.3, presenting Kaplan-Meier curves. DPP-4 inhibitors and sulfonylureas were associated with lower rates of weight loss. Compared to sulfonylureas, GLP-

1RA, SGLT2 inhibitors, and DPP-4 inhibitors were significantly more likely to achieve ≥5% weight loss, with aHR of 2.36 (95% CI: 1.75–3.18), 1.99 (95% CI: 1.41–2.81), and 1.50 (95% CI: 1.04–2.16), respectively. Only GLP-1RA and SGLT2 inhibitors were significantly associated with ≥10% weight loss versus sulfonylureas (Table 3.2).

3.5.4 Subgroup analyses of percent weight change for GLP-1RA and SGLT2 inhibitors

Subgroup analyses are illustrated in Figure 3.2. Among GLP-1RA users, percent weight loss was greater in PWH without diabetes (−6.68% vs. −3.13%; interaction-p=0.002) and in those with BMI ≥35 compared to BMI <30 (−5.61% vs. −1.93%; interaction-p=0.002). Weight loss by specific GLP-1RA agents varied, with semaglutide showing the largest reduction (−5.53%, 95% CI: −7.06 to −4.00), followed by liraglutide (−3.46%, 95% CI: −5.73 to −1.18) and dulaglutide (−2.66%, 95% CI: −4.60 to −0.71).

Among SGLT2 inhibitor users, significant weight loss was observed only in PWH with diabetes, while no significant change was seen in those without diabetes; however, the difference between diabetes status groups was not statistically significant despite trends toward greater loss in those with diabetes. Weight loss was also significantly greater in people with BMI ≥35 compared to those with BMI <30 (interaction-p=0.003). No significant differences by sex or age were observed in either treatment group. Some subgroup differences may have been undetected due to limited power.

3.5.5 Sensitivity analyses

Results from the ITT analysis were directionally consistent but slightly attenuated compared to the primary on-treatment findings (Supplemental Table 3.2). Restricting to people with diabetes yielded a similar pattern of weight change across medication groups (Supplemental Table 3.3).

3.5.6 Long-term weight change trajectories beyond 1 year

Additional analyses to explore long-term weight trajectories showed that weight change trends were nonlinear over time (Supplemental Table 3.4). GLP-1RA users experienced the greatest weight loss in the first 6 months (–5.20%), followed by slower declines between 6–12 months (–3.31%) and beyond 12 months (–2.18%). SGLT2 inhibitor users showed modest initial loss with minimal changes thereafter. DPP-4 inhibitors showed negligible weight change across all time intervals, while sulfonylureas were associated with early weight gain (+2.01% from 0–6 months), followed by a return to baseline weight. For this analysis, the median (IQR) follow-up was 1.00 (0.53–1.72) years for GLP-1RA users, 1.00 (0.63–1.72) for SGLT2 inhibitor users, 1.59 (0.64–3.38) for DPP-4 inhibitor users, and 1.25 (0.50–2.91) for sulfonylurea users, with corresponding means (SD) of 1.34 (1.21), 1.35 (1.26), 2.30 (2.06), and 2.09 (2.18) years, respectively.

3.6 Discussion

This real-world cohort study is among the first to evaluate the impact of various antidiabetic medications on weight change in PWH, a population increasingly burdened by cardiometabolic diseases including obesity. Our results show that treatment with GLP-1RA was associated with the greatest and most significant weight loss, particularly in people without diabetes and those with higher BMI, with around half of the GLP-1RA users achieving ≥5% weight loss at 1 year. Treatment with SGLT2 inhibitors also was associated with moderate weight loss benefits, while DPP-4 inhibitors and sulfonylureas had minimal impact on weight.

Our findings are broadly consistent with existing clinical trial evidence in the general population and align with the limited but emerging literature among PWH, where GLP-1RA, particularly semaglutide, have shown a promising effect on weight loss.[20–22,26] For example, two small clinical

trials of semaglutide 1 mg in PWH without diabetes reported mean weight reductions of around 8%,[20,26] which exceed the mean reduction observed in our study (-5.0 kg or -4.4%). This difference is expected given the distinctions between trial settings and real-world practice. In addition, although most individuals in our GLP-1RA group were prescribed semaglutide, some received older agents such as dulaglutide, which are associated with smaller weight reductions. Additionally, in routine clinical practice, patients may receive lower doses and not be titrated to the maximum effective dose, which could further attenuate observed effects. Moreover, our findings align with a retrospective real-world cohort study among 225 PWH treated with GLP-1RA that reported an average weight loss of 5.4 kg with 44% achieving ≥5% weight loss at 13 months.[21] Furthermore, the weight change observed in our additional analysis of percent weight change over time showed that GLP-1RA had a trajectory of rapid initial weight loss, followed by slower reduction mirroring patterns observed in the general population.[27,28] Similarly, for SGLT2 inhibitors, although evidence in PWH remains limited, our results similarly align with findings from the general population. The weight loss of approximately 1.3 kg observed in our cohort is comparable to prior studies in non-HIV populations, where SGLT2 inhibitors typically lead to weight reductions of around 1-3 kg.[29,30]

In subgroup analyses, greater weight loss with GLP-1RA treatment occurred among people with higher baseline BMI and those without diabetes. These trends are consistent with findings in both the general population and PWH.[21,31] This finding likely reflects clinician prescribing practices, as people without diabetes are often prescribed higher-dose GLP-1RA such as semaglutide for obesity management and may also be more motivated to adopt lifestyle changes. In people with diabetes, weight loss may be blunted by concurrent use of medications such as insulin that are

associated with weight gain.[27,32] In contrast, among users of SGLT2 inhibitors, weight loss appeared slightly greater among those with diabetes, although this difference was not statistically significant, likely due to limited power. This pattern has been observed previously in the general population, as SGLT2 inhibitor-induced weight loss largely results from glycosuria, which is greater in individuals with higher baseline glucose levels (i.e., those with diabetes) experiencing greater caloric loss.[33] People without diabetes who are prescribed SGLT2 inhibitors for heart failure or CKD, may experience less weight loss due to attenuated glycosuria, particularly in CKD.[34]

Given the rising prevalence of overweight and obesity among PWH, these findings highlight the potential role of newer antidiabetic medication classes in weight management. GLP-1RA, due to their superior weight loss effects, should be prioritized for PWH with obesity or metabolic comorbidities, whereas SGLT2 inhibitors may offer modest benefits, particularly in those with diabetes. Also, the degree of weight loss observed with GLP-1RA in our cohort was clinically meaningful, with nearly half achieving ≥5% weight loss, a threshold associated with improvements in glycemic control, blood pressure, lipid levels, and liver fat accumulation.[35] More substantial reductions of ≥10%, achieved by over one in four GLP-1RA users, have been linked to even greater benefits including resolution of metabolic dysfunction-associated steatohepatitis (MASH) and lower risk of cardiovascular events,[35] outcomes that are especially relevant for PWH. However, further research is needed to determine whether these weight loss effects translate into actual reductions in cardiovascular events and liver disease progression in this population.

Despite their promise, significant barriers to broader adoption of these medications remain, including limited access due to drug shortages and affordability challenges, especially when GLP-1RA are prescribed for obesity management. These challenges are amplified among populations

experiencing healthcare inequities, such as racialized groups.[36] Additionally, gastrointestinal side effects often lead to early discontinuation of GLP-1RA,[37] limiting long-term adherence and benefits. There is also ongoing concern regarding lean muscle mass loss with GLP-1RA,[38] which may be especially relevant in PWH given their elevated risk for sarcopenia.[39,40] Limited trial data in PWH suggest some muscle loss may occur, but physical function is generally preserved.[41] Further research is needed to better characterize the long-term effects on muscle mass and function in this population. These considerations highlight the need for individualized treatment decisions and equity-focused strategies to improve access to effective obesity pharmacotherapy in HIV care.

3.6.1 Limitations

Our study benefits from a large, diverse real-world cohort of PWH, but several limitations warrant consideration. First, as in any observational study, residual confounding remains possible despite the use of an active-comparator, new-user design and multivariable regression adjustment. In our study, this could arise from channeling bias, where certain treatments are preferentially prescribed to patients with specific characteristics; for example, PWH with higher BMI were more likely to receive GLP-1RA than other classes. Dietary intake and physical activity were not incorporated into our analysis because only limited lifestyle information is collected in CNICS, and these data are incomplete and inconsistently captured across sites, contributing to potential unmeasured residual confounding, particularly if individuals initiating GLP-1RA were more likely to receive lifestyle counseling or engage in behavior change. Second, our primary on-treatment analysis censored follow-up at medication discontinuation or switching, which may introduce informative censoring bias since treatment changes can often relate to treatment non-response.

To better reflect real-world effectiveness, we conducted an ITT sensitivity analysis, which included all weight measurements regardless of treatment changes and provided a conservative estimate of treatment effects. Third, weight ascertainment was not standardized across clinical sites. Differences in scale models, calibration procedures, and protocols regarding clothing or footwear may introduce additional measurement variability. Fourth, inclusion in the primary analysis required at least one baseline weight and at least one follow-up weight within 1 year to estimate 1-year weight change, which may introduce selection bias, as individuals with more complete weight recording may differ systematically from those without follow-up measurements. In addition, not all PWH had follow-up weights beyond 1 year, meaning long-term weight change estimates rely on fewer observations and may be less precise and potentially subject to selection bias. Fifth, although we examined various GLP-1RA agents, we did not assess dose–response effects due to limited sample size and missing dose information, and tirzepatide was not included as it was not widely used during the study period. Finally, our findings may be most generalizable to PWH engaged in routine clinical care.

3.7 Conclusion

In conclusion, among PWH, a population at high risk for obesity and cardiovascular disease, we found that GLP-1RA were associated with the largest and clinically significant mean weight loss, in particular among those without diabetes or with higher BMI. On the other hand, SGLT2 inhibitors offered more modest weight loss benefits primarily in people with diabetes, but their role as a standalone therapy for obesity management may be limited. Both remain valuable treatment options, with GLP-1RA preferred for targeted weight management. Further research is

needed to confirm the long-term durability of weight loss with these agents and to explore the wider cardiometabolic benefits of these therapies in this high-risk population of PWH.

3.8 Tables and Figures

Table 3.1. Baseline Characteristics of PWH by Antidiabetic Medication Class

Characteristic	GLP-1RA (n = 619)	SGLT2i (n = 290)	DPP-4i (n = 199)	Sulfonylurea (n = 464)	Total (N = 1,572)
Age, mean (SD)	51.5 (10.3)	55.8 (9.7)	56.2 (10.3)	52.6 (10.0)	53.2 (10.3)
Sex, n (%)					
Male	452 (73.0)	233 (80.3)	142 (71.4)	355 (76.5)	1,182 (75.2)
Female	167 (27.0)	57 (19.7)	57 (28.6)	109 (23.5)	390 (24.8)
Race, n (%)					
White	241 (38.9)	103 (35.5)	69 (34.7)	146 (31.5)	559 (35.6)
Black	238 (38.5)	147 (50.7)	106 (53.3)	239 (51.5)	730 (46.4)
Hispanic	111 (17.9)	26 (9.0)	17 (8.5)	63 (13.6)	217 (13.8)
Other	29 (4.7)	14 (4.8)	7 (3.5)	16 (3.4)	66 (4.2)
Diabetes, n (%)	369 (59.6)	195 (67.2)	199 (100.0)	464 (100.0)	1,227 (78.1)
HbA1c, mean (SD), %	7.1 (2.3)	7.2 (2.2)	8.0 (2.0)	8.7 (2.3)	7.7 (2.3)
Weight, mean (SD), kg	110.2 (24.8)	92.6 (23.6)	95.2 (25.6)	94.6 (22.5)	100.5 (25.3)
BMI, mean (SD), kg/m²	36.3 (7.8)	30.8 (8.2)	32.1 (8.9)	31.5 (7.5)	33.3 (8.3)
BMI Category, n (%)					
< 30	115 (18.6)	159 (54.8)	99 (49.7)	217 (46.8)	590 (37.5)
30 - 34.9	181 (29.2)	56 (19.3)	52 (26.1)	124 (26.7)	413 (26.3)
≥ 35	316 (51.1)	74 (25.5)	48 (24.1)	120 (25.9)	558 (35.5)
eGFR, mean (SD), mL/min/1.73m²	83.6 (22.4)	71.6 (23.6)	72.3 (25.9)	86.0 (23.2)	80.7 (24.1)
Hypertension, n (%)	410 (66.2)	213 (73.5)	153 (76.9)	292 (62.9)	1,068 (68.0)
HIV Viral Load < 200 cells/mm³, n (%)	589 (95.1)	262 (90.3)	188 (94.5)	414 (89.2)	1,453 (92.4)
CD4 Count, mean (SD), cells/mm³	790.6 (384.1)	663.0 (375.5)	704.3 (377.9)	688.0 (383.9)	725.8 (385.1)
ART use, n (%)	603 (97.4)	282 (97.2)	196 (98.5)	443 (95.5)	1,524 (97.0)
TAF use, n (%)	407 (65.8)	172 (59.3)	90 (45.2)	150 (32.3)	819 (52.1)
INSTI use, n (%)	492 (79.5)	236 (81.4)	152 (76.4)	312 (67.2)	1,192 (75.8)
TDF use, n (%)	526 (85.0)	249 (85.9)	151 (75.9)	293 (63.2)	1,219 (77.5)
Metformin use, n (%)	264 (42.7)	116 (40.0)	101 (50.8)	308 (66.4)	789 (50.2)
Insulin use, n (%)	109 (17.6)	69 (23.8)	35 (17.6)	70 (15.1)	283 (18.0)
Statin use, n (%)	342 (55.3)	198 (68.3)	134 (67.3)	239 (51.5)	913 (58.1)
Antipsychotic use, n (%)	116 (18.7)	43 (14.8)	25 (12.6)	62 (13.4)	246 (15.7)
Cigarette smoking, n (%)	216 (34.9)	135 (46.6)	72 (36.2)	166 (35.8)	589 (37.5)

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.

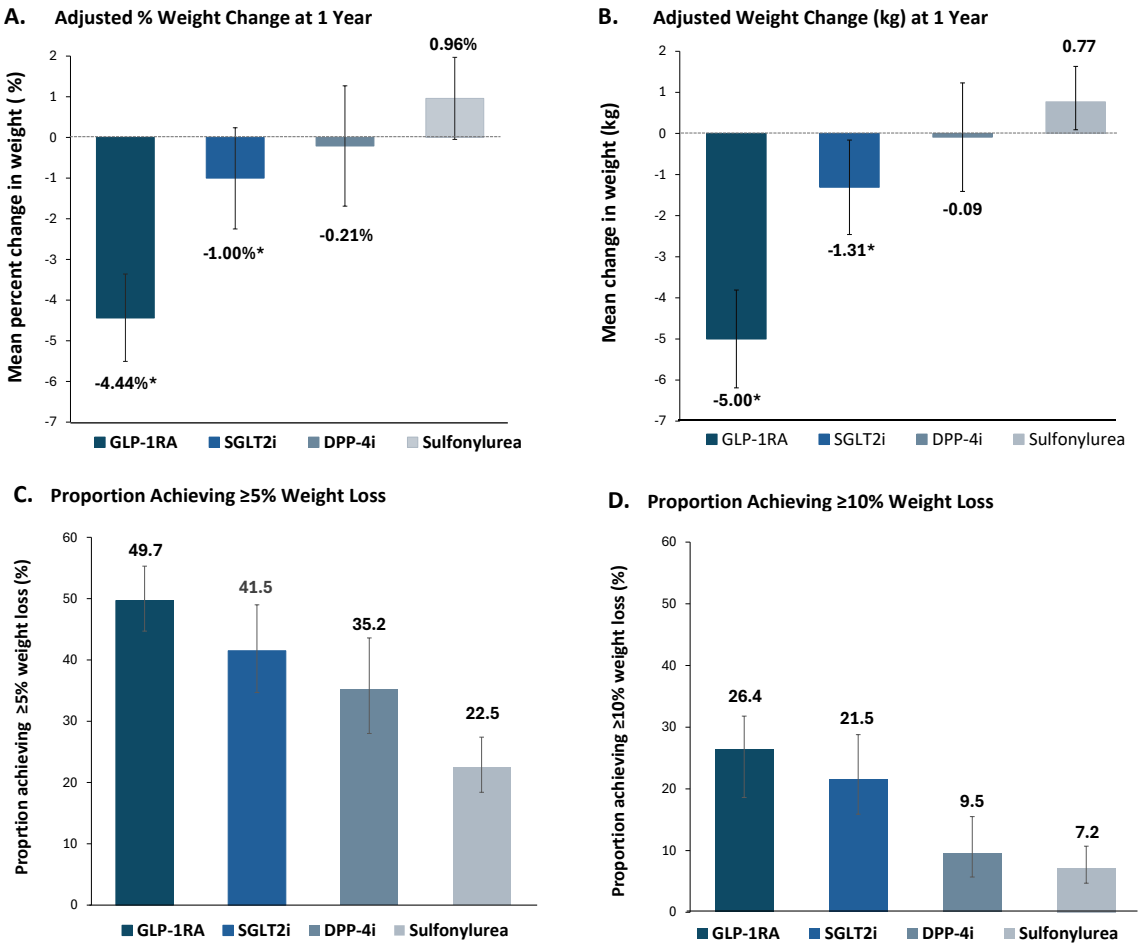
Table 3.2. Primary and Secondary Weight Outcomes at 1 Year by Antidiabetic Medication Class (N=1,572)

Outcome	GLP-1RA (n = 619)	SGLT2i (n = 290)	DPP-4i (n = 199)	Sulfonylurea (n = 464)
Primary Outcome				
Weight Change (%) at 1 year	-4.44 (-5.51, -3.36)	-1.00 (-2.25, 0.24)	-0.21 (-1.68, 1.27)	0.96 (-0.05, 1.97)
Between-treatment difference vs sulfonylurea* (95% CI, *p*-value)	-5.40 (-6.85, -3.94), *p* < 0.001	-1.96 (-3.55, -0.38), *p* = 0.02	-1.16 (-2.93, 0.60), *p* = 0.2	Reference
Secondary Outcomes				
Weight Change (kg) at 1 year	-5.00 (-6.19, -3.81)	-1.31 (-2.46, -0.16)	-0.09 (-1.41, 1.23)	0.77 (-0.09, 1.63)
Between-treatment difference vs sulfonylurea* (95% CI, *p*-value)	-5.77 (-7.22, -4.31), *p* < 0.001	-2.08 (-3.50, -0.65), *p* = 0.004	-0.85 (-2.42, 0.71), *p* = 0.3	Reference
Proportion ≥5% Weight Loss at 1 Year (%)	49.7 (44.7, 55.3)	41.5 (34.7, 49.0)	35.2 (28.0, 43.6)	22.5 (18.4, 27.4)
aHR (95% CI) for ≥5% Weight Loss	2.36 (1.75, 3.18)	1.99 (1.41, 2.81)	1.50 (1.04, 2.16)	Reference
Proportion ≥10% Weight Loss at 1 Year (%)	26.4 (18.6, 31.8)	21.5 (15.9, 28.8)	9.5 (5.7, 15.5)	7.2 (4.7, 10.7)
aHR (95% CI) for ≥10% Weight Loss	3.05 (1.84, 5.03)	2.26 (1.26, 4.06)	1.18 (0.60, 2.31)	Reference

**p*-values reflect between-group comparisons versus sulfonylurea using adjusted linear mixed models.

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; aHR, adjusted hazard ratio; CI, confidence interval.

Figure 3.1. One-Year Weight Change Outcomes by Antidiabetic Medication Class



Legend for Figure 3.1

Panel A shows adjusted percent weight change (%) at 1 year, estimated using linear mixed-effects models adjusted for age, sex, race/ethnicity, study site, hypertension, diabetes, eGFR, weight, CD4 cell count, HIV viral load, smoking, and medication use (ART, antipsychotics, statins, insulin, metformin).

Panel B shows adjusted absolute weight change (kg) at 1 year, using linear mixed-effects models and covariates as in Panel A.

Panel C shows 1-year cumulative incidence of ≥5% weight loss with 95% confidence intervals, derived from Kaplan–Meier analysis.

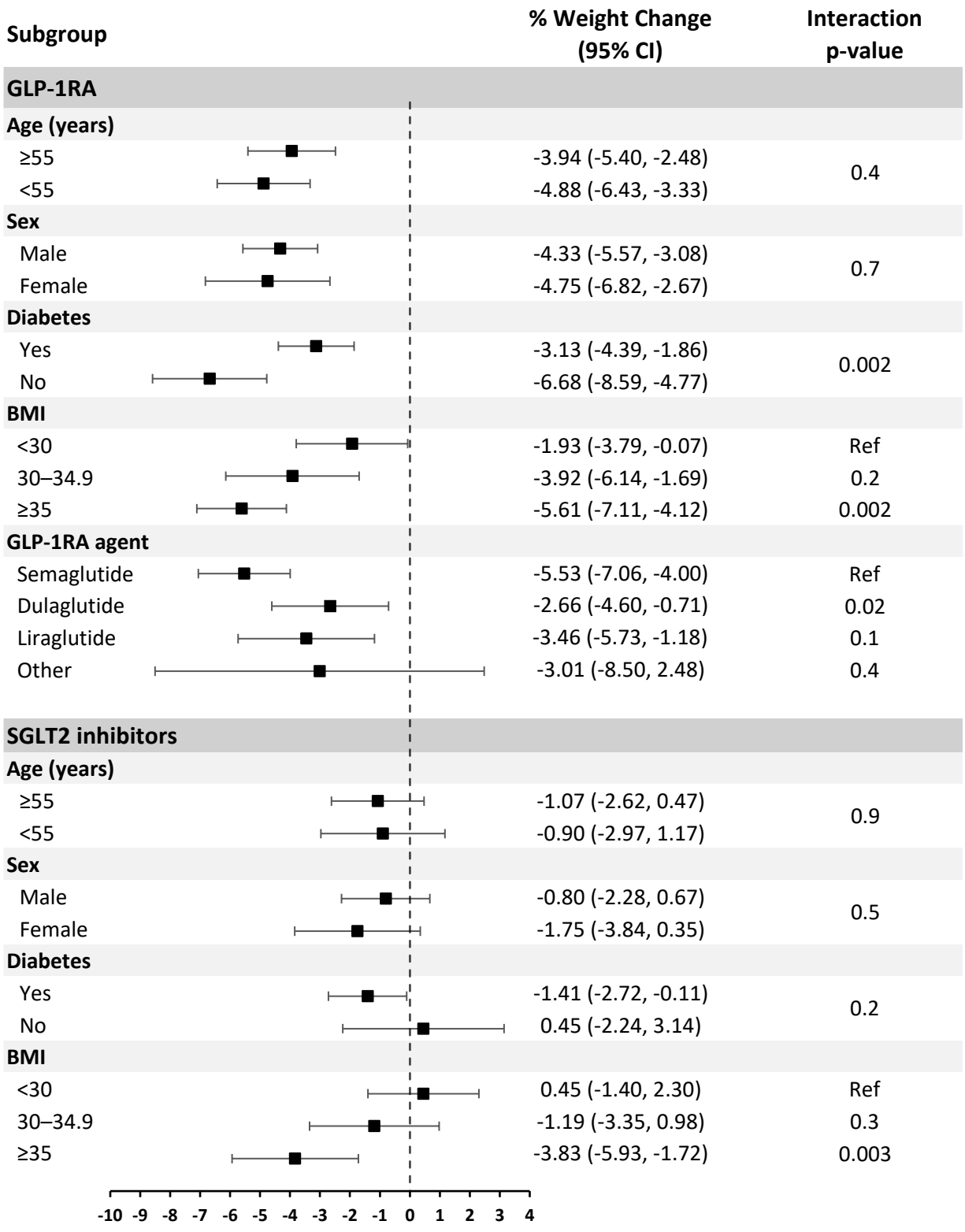
Panel D shows 1-year cumulative incidence of ≥10% weight loss, estimated in the same manner as Panel C.

Error bars represent 95% CIs.

Asterisks (*) indicate statistically significant differences compared with sulfonylurea ($P < 0.05$).

Abbreviations: GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase 4 inhibitor.

Figure 3.2. Within-Class Subgroup Analyses of Adjusted Mean Percentage Weight Change for GLP-1RA and SGLT2 Inhibitor Users

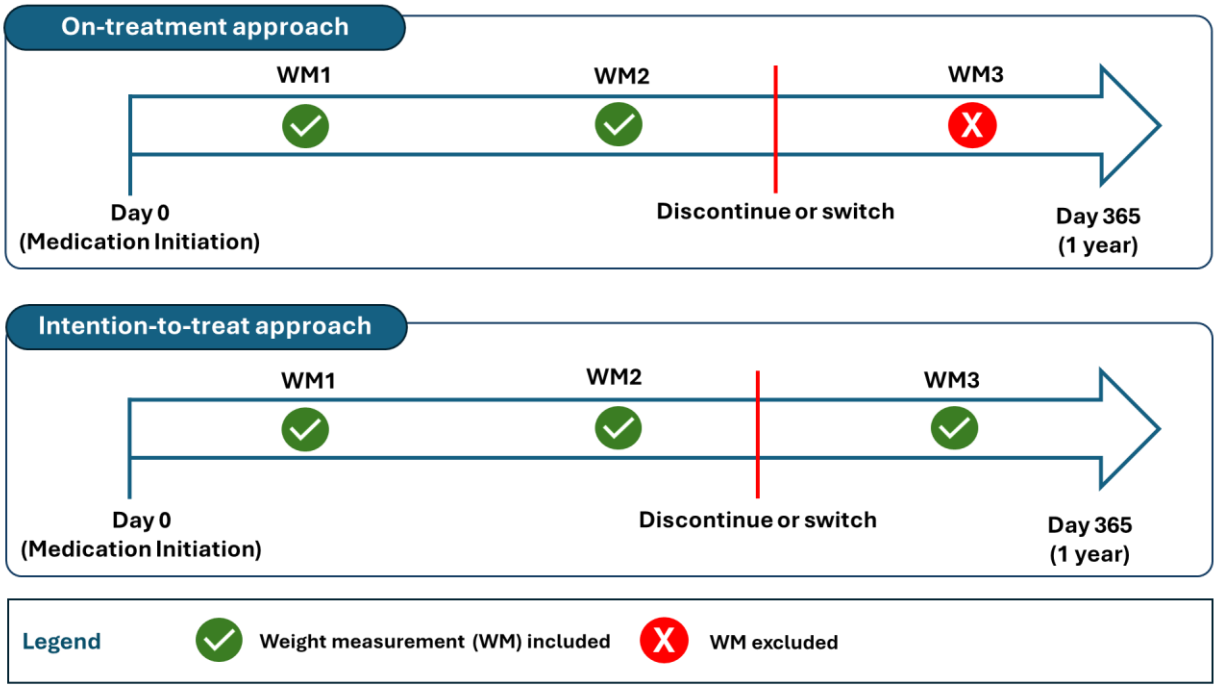


Legend for Figure 3.2. Adjusted mean percentage weight change and 95% confidence intervals are shown for subgroups of PWH initiating GLP-1 receptor agonists (top panel) or SGLT2 inhibitors (bottom panel). Estimates derived from linear mixed models including random intercepts and slopes for time, adjusted for age, sex, race and ethnicity, CNICS site, smoking history, diabetes, hypertension, baseline weight, estimated glomerular filtration rate (eGFR), CD4 cell count, HIV viral load (log_{10}), and use of antiretroviral therapy, statins, antipsychotics, metformin, and insulin.

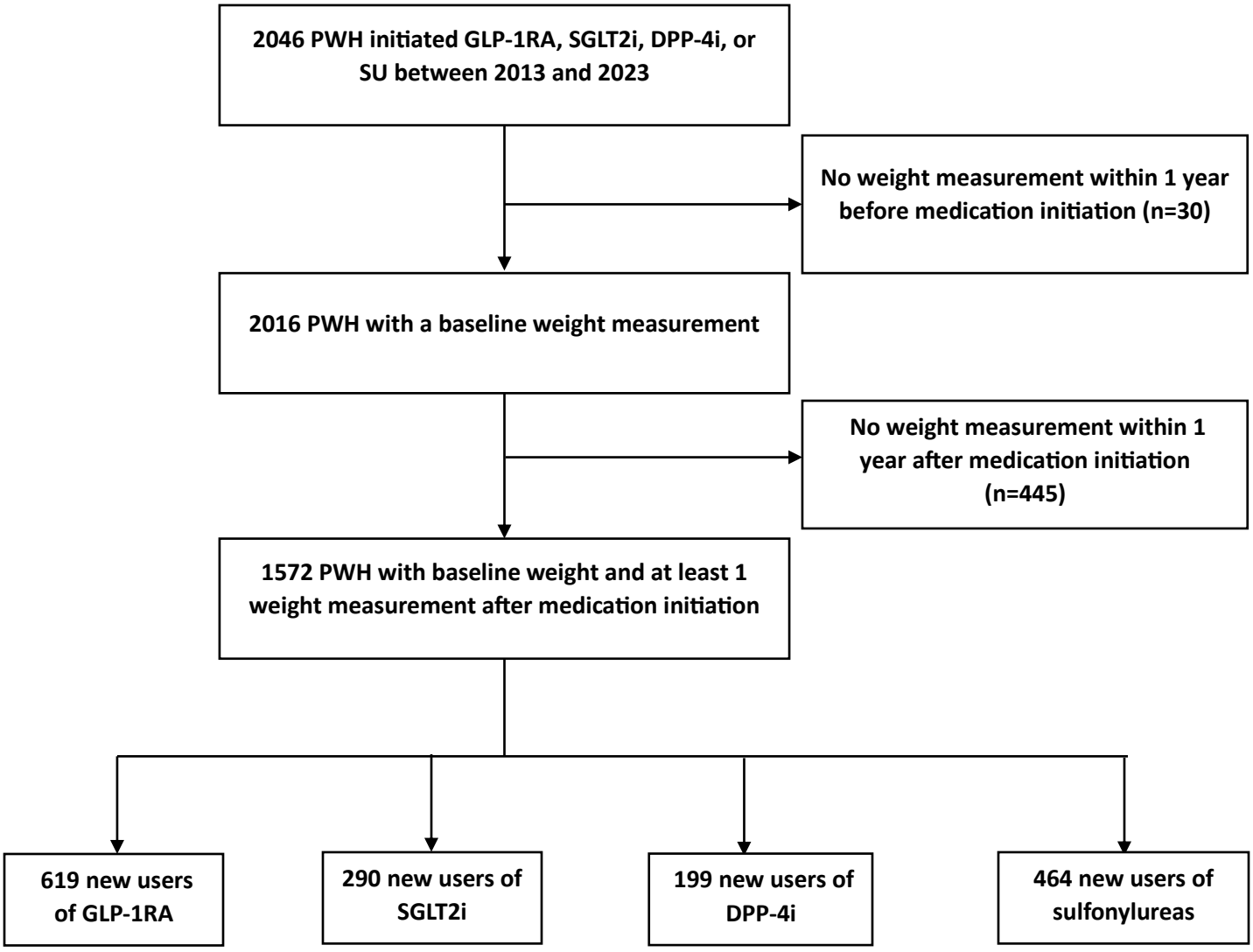
Abbreviations: GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT2, sodium–glucose cotransporter 2; BMI, body mass index.

3.9 Supplementary Tables and Figures

Supplemental Figure 3.1. Comparison of On-Treatment and Intention-to-Treat Analytic Approaches



Supplemental Figure 3.2. Flowchart of Cohort Selection



Supplemental Table 3.1. Antidiabetic Medications Included by Antidiabetic Class

Class	Included Medications
GLP-1RA	Dulaglutide, Exenatide, Semaglutide (oral & injectable), Liraglutide, Liraglutide, Liraglutide, Lixisenatide, Albiglutide
SGLT2 Inhibitors	Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin
DPP-4 Inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
Sulfonylureas	Glyburide, Glimepiride, Glipizide

Supplemental Table 3.2. Intention-to-Treat Analysis of 1-Year Percent Weight Change by Antidiabetic Medication Class

Class	N	N observations	Adjusted Mean % Weight Change (95% CI)	p-value vs. Sulfonylurea
GLP-1RA	619	3051	-3.84% (-4.81, -2.88)	<0.001
SGLT2i	290	1743	-1.07% (-2.20, 0.05)	0.03
DPP-4i	199	1140	0.37% (-1.28, 2.03)	0.9
Sulfonylurea	464	2982	0.53% (-0.37, 1.43)	Reference

Supplemental Table 3.3. Adjusted Mean Percent Weight Change by Medication Class Among People with Diabetes (n = 1,227)

Class	N	N observations	Adjusted Mean % Weight Change (95% CI)	p-value vs. Sulfonylurea
GLP-1RA	369	1708	-3.31% (-4.57, -2.05)	<0.001
SGLT2i	195	975	-1.76% (-3.09, -0.43)	0.009
DPP-4i	199	917	-0.18% (-1.66, 1.30)	0.8
Sulfonylurea	464	2235	1.05% (0.04, 2.05)	Reference

Supplemental Table 3.4. Adjusted Mean Percent Weight Change Estimates from Linear Mixed Models and Spline-Based Mixed Models with Knots at 6 and 12 Months

Model	GLP-1RA	SGLT2i	DPP-4i	Sulfonylurea
Primary Analysis	**-4.44 (-5.51, -3.36)**	-1.00 (-2.25, 0.24)	-0.21 (-1.69, 1.27)	0.96 (-0.05, 1.97)
1-Year Follow-Up				
Exploratory Analysis				
Piecewise Linear Spline with Knots at 6 and 12 Months, 3-Year Maximum Follow-Up				
0–6 months	-5.20 (-6.56, -3.84)	-1.54 (-3.40, 0.32)	-0.53 (-3.15, 2.09)	2.04 (0.62, 3.45)
6–12 months	-3.31 (-5.10, -1.53)	-0.01 (-2.22, 2.20)	0.08 (-1.96, 2.13)	-1.17 (-2.59, 0.24)
>12 months	-2.18 (-3.21, -1.15)	-0.25 (-2.61, 2.11)	-0.82 (-1.94, 0.30)	-1.35 (-2.05, -0.66)

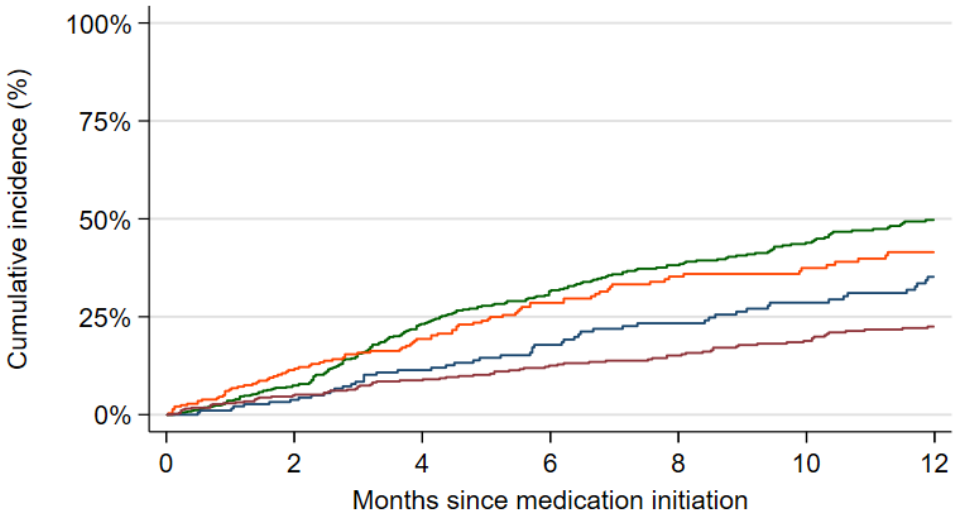
Notes:

- Values are mean percent weight change (95% confidence intervals) from mixed models.
- Analyses were conducted using on-treatment follow-up. Participants without at least one weight measurement within 1 year of initiating their antidiabetic medication were excluded from both the primary and exploratory models

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor

Supplemental Figure 3.3. Unadjusted Kaplan-Meier Curves for Time to ≥5% and ≥10% Weight Loss

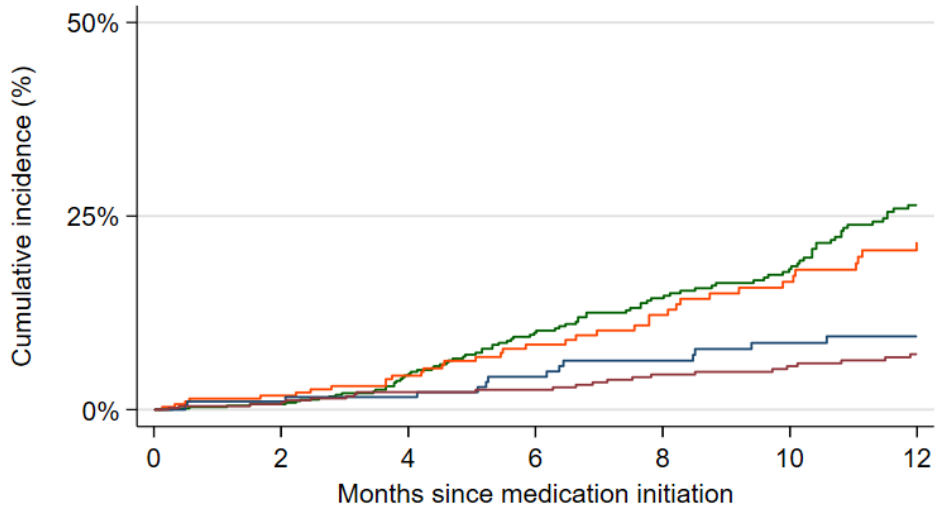
A. ≥5% weight loss



Number at risk

GLP-1RA	619	480	339	264	204	163	127
SGLT2i	290	225	178	132	96	82	65
DPP-4i	199	171	145	122	104	89	78
Sulfonylurea	464	384	334	286	257	227	200

B. ≥10% weight loss



Number at risk

GLP-1RA	619	508	405	331	266	222	167
SGLT2i	290	246	205	163	129	108	82
DPP-4i	199	175	158	139	125	112	104
Sulfonylurea	464	395	349	312	281	255	230

3.10 Contributions of Authors:

L.H., R.M.N., H.M.C., S.E., and J.A.C.D. contributed to the design of the study and analysis plan, with L.H. and R.M.N. performing the statistical analyses. L.H. drafted the initial manuscript, and all authors contributed to critical revisions and approved the final version. The authors gratefully acknowledge all CNICS participants and study personnel for their essential contributions to this work.

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3.12 Additional Results (Not Included in the Submitted Manuscript)

In addition to the results reported in the manuscript and its supplementary materials, the following analyses were conducted to complement the findings presented in this chapter. These results were not included in the submitted paper but are presented here to provide additional context and depth for the thesis. Unless otherwise specified, the data were derived from the same study population and analytic framework described earlier in this chapter.

3.12.1 Assessment of Potential Bias Due to Missing Follow-up Weight Data

To assess potential bias related to missing follow-up weight data, baseline characteristics of participants included versus excluded were compared across medication classes (Additional Table 3.1). Participants excluded due to missing follow-up weight were largely similar to those included across medication classes, with only modest differences in select clinical and demographic characteristics. These differences suggest that follow-up weights were missing at random, but the overall similarity between groups indicates that any resulting bias in estimated weight change is likely minimal.

Additional Table 3.1. Baseline characteristics of participants included vs excluded for missing follow-up weight, stratified by medication class

Characteristic	GLP-1RA Excluded (n=233)	GLP-1RA Included (n=619)	P	SGLT2i Excluded (n=63)	SGLT2i Included (n=290)	P	DPP-4i Excluded (n=41)	DPP-4i Included (n=199)	P	SU Excluded (n=107)	SU Included (n=464)	P
Continuous variables (mean ± SD)												
Age (years)	51.17 ± 10.73	51.51 ± 10.25	0.674	58.4 ± 9.3	55.8 ± 9.7	0.054	54.6 ± 9.7	56.2 ± 10.3	0.368	53.2 ± 10.4	52.6 ± 10.0	0.587
Baseline weight (kg)	110.0 ± 27.9	110.2 ± 24.8	0.923	93.0 ± 25.5	92.6 ± 23.6	0.919	95.4 ± 18.0	95.2 ± 25.6	0.947	94.6 ± 27.5	94.6 ± 22.5	0.998
$\log_{10}$ Viral load	1.59 ± 1.00	1.59 ± 0.96	0.999	1.64 ± 1.00	1.64 ± 1.10	0.999	1.55 ± 0.91	1.60 ± 1.07	0.795	1.91 ± 1.21	1.64 ± 1.03	0.018
Baseline CD4 (cells/mm³)	759.4 ± 350.1	787.2 ± 383.8	0.334	620.9 ± 392.8	662.6 ± 374.2	0.427	848.8 ± 535.3	698.0 ± 386.3	0.035	629.9 ± 371.1	684.6 ± 384.5	0.183
Baseline HbA1c (%)	6.76 ± 1.93	7.12 ± 2.30	0.035	7.06 ± 1.95	7.25 ± 2.19	0.527	7.64 ± 1.89	7.99 ± 2.02	0.318	8.66 ± 2.68	8.71 ± 2.26	0.848
Baseline eGFR (mL/min/1.73 m²)	83.99 ± 21.61	83.63 ± 22.45	0.829	72.5 ± 24.6	71.6 ± 23.6	0.776	79.1 ± 23.0	72.3 ± 25.9	0.118	87.0 ± 23.8	86.0 ± 23.2	0.684
Categorical variables (n, %)												
Female	65 (27.9)	167 (27.0)	0.788	9 (14.3)	57 (19.7)	0.322	10 (24.4)	57 (28.6)	0.580	24 (22.4)	109 (23.5)	0.815

Race			0.220			0.219			0.775			0.007
– White	102 (43.8)	241 (38.9)		30 (47.6)	103 (35.5)		16 (39.0)	69 (34.7)		32 (29.9)	146 (31.5)	
– Black	82 (35.2)	238 (38.5)		23 (36.5)	147 (50.7)		19 (46.3)	106 (53.3)		42 (39.3)	239 (51.5)	
– Hispanic	33 (14.2)	111 (17.9)		6 (9.5)	26 (9.0)		5 (12.2)	17 (8.5)		24 (22.4)	63 (13.6)	
– Other	16 (6.9)	29 (4.7)		4 (6.3)	14 (4.8)		1 (2.4)	7 (3.5)		9 (8.4)	16 (3.5)	
Currently on ART	227 (97.4)	603 (97.4)	0.994	62 (98.4)	282 (97.2)	0.593	38 (92.7)	196 (98.5)	0.030	101 (94.4)	443 (95.5)	0.635
On TDF	33 (14.2)	93 (15.0)	0.752	11 (17.5)	41 (14.1)	0.500	6 (14.6)	48 (24.1)	0.185	34 (31.8)	171 (36.9)	0.324
On TAF	159 (68.2)	407 (65.8)	0.493	46 (73.0)	172 (59.3)	0.042	21 (51.2)	90 (45.2)	0.483	45 (42.1)	150 (32.3)	0.056
Antipsychotic use	28 (12.0)	116 (18.7)	0.020	12 (19.1)	43 (14.8)	0.403	4 (9.8)	25 (12.6)	0.616	14 (13.1)	62 (13.4)	0.939
Statin use	102 (43.8)	342 (55.3)	0.003	42 (66.7)	198 (68.3)	0.804	21 (51.2)	134 (67.3)	0.049	49 (45.8)	239 (51.5)	0.287
Smoking	81 (34.8)	216 (34.9)	0.971	25 (39.7)	135 (46.6)	0.321	13 (31.7)	72 (36.2)	0.585	46 (43.0)	166 (35.8)	0.164
Hypertension	146 (62.7)	410 (66.2)	0.329	41 (65.1)	213 (73.5)	0.180	26 (63.4)	153 (76.9)	0.071	63 (58.9)	292 (62.9)	0.436
Insulin use	17 (7.3)	79 (12.8)	0.024	3 (4.8)	46 (15.9)	0.021	6 (14.6)	21 (10.6)	0.451	13 (12.1)	41 (8.8)	0.291
Metformin use	57 (24.5)	188 (30.4)	0.089	19 (30.2)	87 (30.0)	0.980	11 (26.8)	70 (35.2)	0.303	57 (53.3)	212 (45.7)	0.157
Diabetes	124 (53.2)	369 (59.6)	0.117	41 (65.1)	195 (67.2)	0.653	41 (100)	199 (100)	—	107 (100)	464 (100)	—

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor

3.12.2 Additional Spline Model Estimates of Weight Change

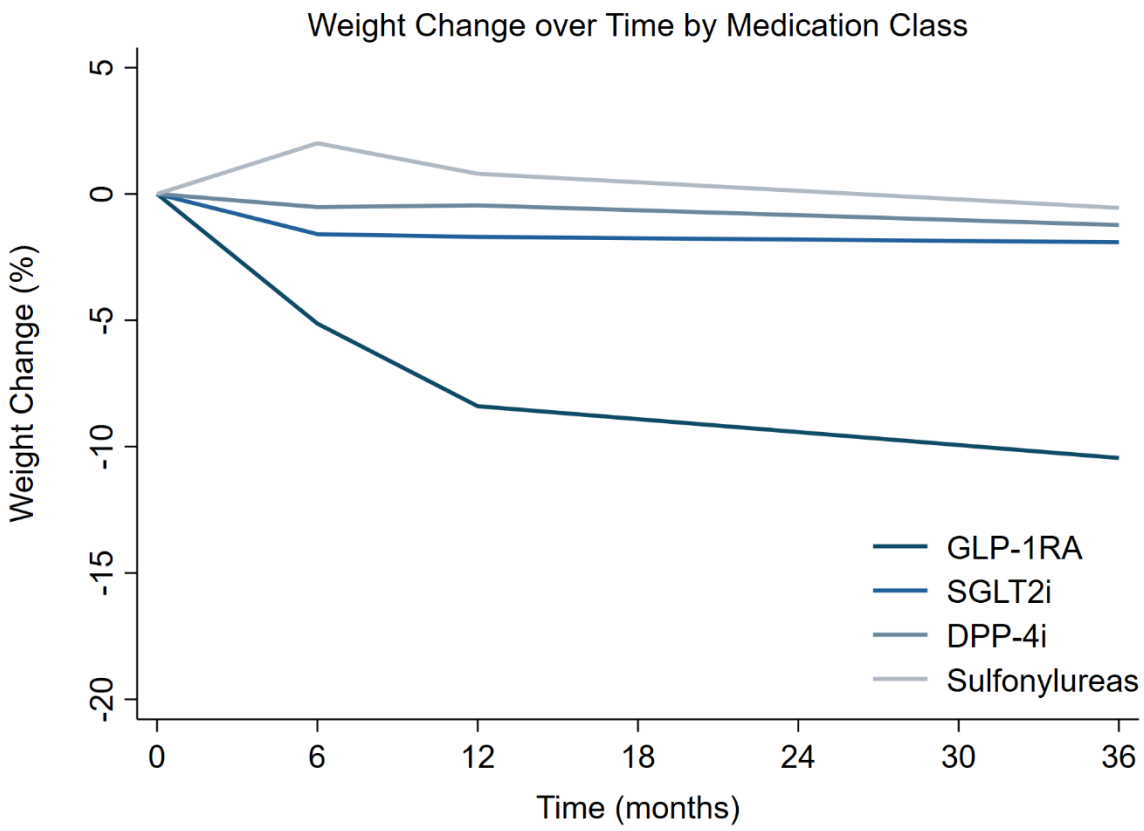
Additional Table 3.2 provides estimates of percent weight change using piecewise spline models with three specifications: a single knot at 6 months, a single knot at 12 months, and two knots at 6 and 12 months. These models capture potential non-linear patterns in weight change by allowing the slope to change at specified time points (the "knots"), resulting in different linear slopes within each time interval. Additional Figure 3.1 visualizes 3-year weight trajectories by medication class using a piecewise spline model with knots at 6 and 12 months.

Additional Table 3.2. Percent Weight Change Estimates from Linear Mixed Models and Spline-Based Mixed Models with Knots at 6 and/or 12 Months

Model	GLP-1RA	SGLT2i	DPP-4i	Sulfonylurea
Primary Analysis (1-Year Follow-Up)	-4.44 (-5.51, -3.36)	-1.00 (-2.25, 0.24)	-0.21 (-1.69, 1.27)	0.96 (-0.05, 1.97)
Piecewise Linear Spline Models (3-Year Maximum Follow-up; n=1572)				
Knot at 6 months				
0–6 mo	-5.45 (-6.88, -4.02)	-1.41 (-3.44, 0.62)	-0.05 (-2.64, 2.55)	2.37 (0.89, 3.86)
>6 mo	-2.77 (-3.69, -1.85)	-0.33 (-1.46, 1.79)	-0.66 (-1.46, 0.14)	-1.45 (-1.97, -0.93)
Knot at 12 months				
0–12 mo	-4.38 (-5.35, -3.42)	-0.99 (-2.17, 0.20)	-0.16 (-1.50, 1.18)	0.46 (-0.42, 1.34)
>12 mo	-1.80 (-2.85, -0.75)	-0.08 (-2.40, 2.24)	-0.77 (-1.87, 0.33)	-1.54 (-2.19, -0.90)
Knot at 6 and 12 months				
0–6 mo	-5.20 (-6.56, -3.84)	-1.54 (-3.40, 0.32)	-0.53 (-3.15, 2.09)	2.04 (0.62, 3.45)
6–12 mo	-3.31 (-5.10, -1.53)	-0.01 (-2.22, 2.20)	0.08 (-1.96, 2.13)	-1.17 (-2.59, 0.24)
>12 mo	-2.18 (-3.21, -1.15)	-0.25 (-2.61, 2.11)	-0.82 (-1.94, 0.30)	-1.35 (-2.05, -0.66)

Note: Values are mean percent weight change (95% confidence intervals) from mixed models.

Additional Figure 3.1. Weight Change Trajectories Over 3 Years by Medication Group Using Piecewise Spline Models with Knots at 6 and 12 Months



Note: Predicted values are additive across intervals and are intended to illustrate general trends and the shape of weight change over time, rather than precise cumulative change estimates at specific time points.

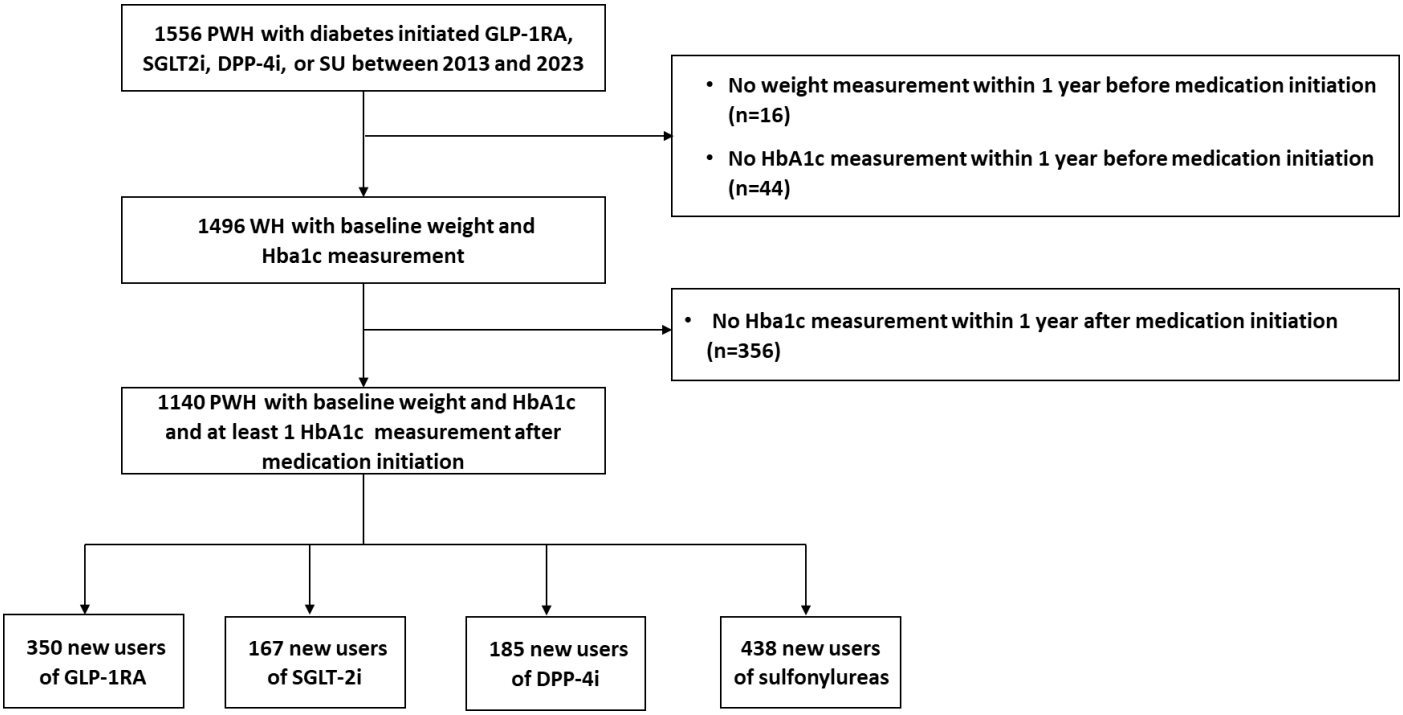
3.12.3 HbA1c Change Results

In addition to evaluating weight change, we examined HbA1c change as a complementary outcome to assess glycemic response, measured as the change in HbA1c following initiation of antidiabetic therapy. A new analytic cohort was created consisting of PWH and diabetes who had adequate HbA1c data available. Specifically, eligible participants had at least one recorded weight and HbA1c measurement within one year before medication initiation and at least one HbA1c measurement within one year after initiation. The selection process for this cohort is illustrated in Additional Figure 3.2. This cohort partially overlaps with, but is distinct from, the primary weight change cohort because inclusion required complete HbA1c data both before and after treatment initiation.

Among 1,140 PWH initiating antidiabetic medications, the cohort was 54 years on average, predominantly male (75%), and racially diverse (Additional Table 3.3). Most were on ART (97%). Comorbidities and concomitant medications, including insulin and metformin, were common. Baseline BMI and weight were highest in the GLP-1RA group. Mean baseline HbA1c ranged from 8.0% (DPP-4i) to 8.8% (sulfonylurea), with an overall mean of 8.4%.

GLP-1RA use was associated with the largest adjusted HbA1c reduction (-1.33%), followed by sulfonylurea (-0.90%), SGLT2i (-0.53%), and DPP-4i (-0.49%). Differences compared to sulfonylurea were not statistically significant (Additional Table 3.4).

Additional Figure 3.2. Flowchart of cohort selection



Additional Table 3.3. Baseline characteristics of PWH by Antidiabetic Medication Class

Characteristic	GLP-1RA (n=350)	SGLT2i (n=167)	DPP-4i (n=185)	Sulfonylurea (n=438)	Total (n=1,140)
Demographics					
Age, mean (SD)	52.99 (10.29)	56.05 (9.67)	55.70 (10.09)	52.60 (10.13)	54.22 (10.21)
Female, n (%)	99 (28.3)	37 (22.2)	55 (29.7)	100 (22.8)	291 (25.5)
Race, n (%)					
White	113 (32.3)	54 (32.3)	64 (34.6)	138 (31.5)	369 (32.4)
Black	167 (47.7)	88 (52.7)	97 (52.4)	217 (49.5)	569 (49.9)
Hispanic	60 (17.1)	18 (10.8)	17 (9.2)	66 (15.1)	161 (14.1)
Other	10 (2.9)	7 (4.2)	7 (3.8)	17 (3.9)	41 (3.6)
HIV-related					
Current ART, n (%)	345 (98.6)	163 (97.6)	182 (98.4)	419 (95.7)	1,109 (97.3)
Current TDF, n (%)	50 (14.3)	26 (15.6)	41 (22.2)	163 (37.2)	280 (24.6)
Current TAF, n (%)	221 (63.1)	102 (61.1)	88 (47.6)	146 (33.3)	557 (48.9)
Comorbidities / Medications					
Antipsychotic use, n (%)	52 (14.9)	23 (13.8)	26 (14.1)	51 (11.6)	152 (13.3)
Statin use, n (%)	233 (66.6)	125 (74.9)	123 (66.5)	227 (51.8)	708 (62.1)
Smoking history, n (%)	128 (36.6)	69 (41.3)	69 (37.3)	161 (36.8)	427 (37.5)
Hypertension treatment, n (%)	249 (71.1)	125 (74.9)	139 (75.1)	282 (64.4)	795 (69.7)
Insulin use, n (%)	103 (29.4)	54 (32.3)	31 (16.8)	70 (16.0)	258 (22.6)
Metformin use, n (%)	226 (64.6)	97 (58.1)	99 (53.5)	302 (69.0)	724 (63.5)
Laboratory / Clinical					
Baseline weight, kg, mean (SD)	109.3 (25.5)	96.3 (22.97)	95.6 (25.7)	94.5 (22.8)	99.7 (25.4)

Baseline BMI, kg/m^2, mean (SD)	36.2 (7.92)	32.6 (8.24)	32.2 (8.92)	31.5 (7.45)	33.4 (8.1)
CD4 count, cells/μL, mean (SD)	789.4 (377.0)	720.2 (375.8)	725.9 (381.4)	698.2 (386.3)	733.6 (379.7)
HIV viral load (log10), mean (SD)	1.39 (0.55)	1.39 (0.65)	1.40 (0.56)	1.45 (0.70)	1.41 (0.60)
Baseline eGFR, mL/min/1.73m^2, mean (SD)	82.0 (23.8)	74.6 (23.4)	72.8 (26.1)	85.9 (22.8)	79.0 (24.5)
Baseline A1c, %	8.21 (2.27)	8.17 (1.98)	8.00 (2.00)	8.80 (2.31)	8.40 (2.23)

Additional Table 3.4. Adjusted Mean Change in HbA1c Among People with HIV and Diabetes, by Antidiabetic Class (n=1140)

Class	N	Adjusted Mean HbA1c (95% CI)	p-value vs. Sulfonylurea
GLP-1RA	350	-1.33 (-1.64, -1.02)	0.06
SGLT2i	167	-0.53 (-0.96, -0.10)	0.2
DPP-4i	185	-0.49 (-0.94, -0.04)	0.1
Sulfonylurea	438	-0.90 (-1.25, -0.55)	Reference

Chapter 4. Impact of SGLT2 Inhibitors on Kidney Function Among People with HIV: A US Prospective Multi-Site Study

4.1 Overview

This manuscript addresses the kidney-related aim of the thesis by examining the impact of sodium-glucose cotransporter 2 inhibitors (SGLT2is) on kidney function among people with HIV (PWH), who are at increased risk for chronic kidney disease but underrepresented in trials.

In a propensity score-matched cohort of 590 PWH (295 SGLT2i users and 295 comparators), early declines in estimated glomerular filtration rate (eGFR) were more common among SGLT2i users. The 6-month incidence of ≥10% eGFR decline was 58.2% versus 37.4% (adjusted hazard ratio [aHR] 1.79; 95% CI 1.40 to 2.28), and ≥30% decline occurred in 17.3 percent versus 9.8 percent (aHR 1.69; 95% CI 1.05 to 2.73). Mean 6-month eGFR change was - 2.62 mL/min/1.73m² in SGLT2i users compared to 0.05 mL/min/1.73m² in comparators, representing small, transient changes consistent with other populations. Longer-term eGFR trajectories over 24 months showed an initial dip followed by stabilization and slower decline, assessed using locally weighted scatterplot smoothing (LOWESS).

These findings show that the early eGFR dip among SGLT2i users, which aligns with the known early hemodynamic effects of this drug class, was transient over longer-term follow-up and may reflect kidney stability rather than harm, although larger studies in PWH are needed to confirm our findings.

Manuscript status: Published

Citation: Haidar L, Crane HM, Nance RM, et al. Impact of SGLT2 Inhibitors on Kidney Function Among People with HIV: A US Prospective Multi-Site Study. *J Acquir Immune Defic Syndr*. Published online February 24, 2026. doi:10.1097/QAI.0000000000003854

Impact of SGLT2 Inhibitors on Kidney Function Among People with HIV: A US Prospective Multi-Site Study

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4.2 Abstract

Background

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are nephroprotective but are associated with early eGFR decline, also termed "eGFR dip." Despite elevated risk of kidney disease, this phenomenon is understudied among people with HIV (PWH).

Methods

In a 1:1 propensity score-matched cohort study using data from 9 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites, we compared new SGLT2i users with new users of other antihyperglycemic classes. We estimated adjusted hazard ratios (aHRs) for time to ≥10% and ≥30% eGFR decline using multivariable Cox proportional hazards models and analyzed eGFR change using multivariable linear mixed models. Additionally, longer-term eGFR trends over 24 months were visualized using locally weighted scatterplot smoothing (LOWESS) curves.

Results

Among 1554 eligible PWH, we obtained 295 matched pairs. Over 6 months, eGFR decline incidence of ≥10% and ≥30% was higher among users of SGLT2i versus other antihyperglycemic classes, (58.2% vs. 37.4%; aHR: 1.79; 95% CI: 1.40-2.28; and 17.3% vs. 9.8%; aHR: 1.69; 95% CI: 1.05-2.73; respectively). Adjusted mean eGFR change at 6 months was −2.62 mL/min/1.73m² for SGLT2i versus 0.05 mL/min/1.73m² for other classes. Long-term eGFR trends revealed an expected initial decline following SGLT2i initiation, followed by stabilization and a slower subsequent decline compared to other classes.

Conclusion

Acute eGFR dips were more common among PWH initiating SGLT2i relative to other antihyperglycemic classes, though overall declines were small, transient, and consistent with the general population. Further research is needed to explore the long-term effects of SGLT2i in PWH.

Keywords: SGLT2 inhibitors; People with HIV; Acute eGFR dip; Antihyperglycemic medications; kidney function

4.3 Introduction

In the past decade, sodium-glucose co-transporter-2 inhibitors (SGLT2i) have received attention for their cardiorenal benefits, with large clinical trials demonstrating a reduction in kidney disease progression, irrespective of diabetes status, and major cardiovascular events.[1–7] Consequently, SGLT2i are of interest for the clinical management of people with HIV (PWH), as cardiovascular disease and chronic kidney disease (CKD) are more prevalent among PWH than the general population, especially as the population of PWH ages. [8–12]

A well-recognized early effect of SGLT2i initiation is an acute, transient decline in estimated glomerular filtration rate (eGFR), commonly referred to as the eGFR "dip," which typically ranges from 3–6 mL/min/1.73m² in the general population and is usually reversible, stabilizing over time.[13–16] This dip primarily reflects hemodynamic changes rather than structural kidney injury. [17] SGLT2 inhibition reduces glucose and sodium reabsorption in the proximal tubule, increasing sodium delivery to the macula densa and triggering tubuloglomerular feedback, which causes afferent arteriole vasoconstriction and lowers intraglomerular pressure.[18] While this mechanism produces an initial eGFR decrease, it may protect against glomerular hyperfiltration and slow long-term kidney function decline.[19] Clinically, SGLT2i discontinuation is generally unnecessary unless an unexplained eGFR decline exceeds 30%.[13,20–23] PWH may be particularly susceptible to acute eGFR changes due to an already elevated risk of renal complications, including CKD and acute kidney injury (AKI), driven by a combination of HIV-specific factors, such as chronic inflammation and antiretroviral therapy (ART), as well as traditional risk factors like diabetes and hypertension.[24] As a result, PWH may require closer monitoring and potential medication adjustments when initiating SGLT2i.

Despite their long-term benefits, SGLT2i are currently underutilized in PWH.[25] Barriers to treatment include potential safety concerns, particularly regarding acute eGFR declines that remain poorly characterized within this population, as well as limited insurance coverage for these medications.[26–28] Such factors may deter clinicians from prescribing SGLT2i, making it crucial to understand these declines. Lack of clinician awareness of this therapeutic class and its benefits may also contribute to under-prescribing.[29] This study characterized the incidence and magnitude of acute eGFR declines within the first 6 months and explored long-term eGFR trends among PWH initiating SGLT2i compared to other antihyperglycemic medication classes.

4.4 Methods

4.4.1 Study Design and Population

We conducted an observational study using data from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort.[30] The CNICS cohort is a dynamic, prospective, clinical cohort of PWH aged 18 and older in care at ten academic sites across the United States. This study includes data from 9 CNICS sites with the necessary data available: University of Washington, Johns Hopkins University, University of Alabama at Birmingham, University of California San Diego, University of North Carolina at Chapel Hill, University of California San Francisco, Case Western Reserve University, Fenway Health, and Vanderbilt University. Sites received local institutional review board approval for participation in CNICS.

PWH who initiated an SGLT2i or other antihyperglycemic medications from the glucagon-like peptide-1 receptor agonist (GLP-1RA), dipeptidyl peptidase-4 inhibitor (DPP-4i), or sulfonylurea classes between 2013 and 2023 were eligible for inclusion. New users were defined as having no previously recorded prescription of any medication within these four classes, with the date of

treatment initiation defined as the index date. To be included, PWH needed to have had at least one eGFR measurement in the year prior to medication initiation, hereafter referred to as the baseline eGFR, and at least one eGFR measurement within 6 months of the index date, hereafter referred to as the post-index eGFR. If a patient had more than one eGFR measurement in the year prior to initiating therapy, the measurement closest to the index date was chosen as the baseline eGFR. PWH with a baseline eGFR <15 mL/min/1.73m², indicative of end-stage renal disease, and those who initiated two or more medications from different antihyperglycemic classes on the index date were excluded.

4.4.2 Outcomes Definitions and Exposure Assessment

Primary outcomes were time to first occurrence of ≥10% and ≥30% decline in eGFR mL/min/1.73m² within the first 6 months following medication initiation. A ≥10% decline was used to capture acute "dipping," whereas a ≥30% decline, a commonly used marker of clinically meaningful kidney function reduction that may warrant closer monitoring or SGLT2i discontinuation, was used to assess more severe declines.

Secondary outcomes included acute eGFR change at 6 months, assessed as the absolute difference between baseline and post-index eGFR measurements, as well as the time to a ≥20% decline in eGFR, and the time to absolute decreases in eGFR of ≥5 and ≥10 mL/min/1.73m². Additionally, we assessed the trajectory of eGFR over 24 months to characterize longer-term trends in eGFR. Exploratory analyses evaluated potential predictors of a ≥10% eGFR decline within 6 months of medication initiation. All analyses compared users of SGLT2i with a combined group of other antihyperglycemic classes, including GLP-1RA, DPP-4 inhibitors, and sulfonylureas. eGFR

was calculated using the race-free 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[31,32]

We identified medication use based on prescription records from routine HIV care visits. Treatment categories included the following: SGLT2i: empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin; GLP-1RA: dulaglutide, exenatide, semaglutide, liraglutide, lixisenatide, and albiglutide; DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, and alogliptin; and sulfonylureas: glyburide, glimepiride, and glipizide.

4.4.3 Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. We computed means and standard deviations (SD) for continuous variables, and calculated frequencies and percentages for categorical variables. When determining follow-up time, we used both an intention-to-treat (ITT) and an on-treatment analysis approach. In the ITT approach, PWH were followed up until the occurrence of the outcome (for time-to-event outcomes), death, or the study end date, defined as 6 months after the index date, whichever occurred first. The on-treatment analysis followed a similar approach but also censored patients at medication discontinuation or switching.

To minimize confounding, we performed 1:1 propensity score (PS) matching to balance covariates between new users of SGLT2i and those initiating other antihyperglycemic classes. Propensity scores were estimated using a logistic regression model that included baseline covariates selected a priori based on their potential to act as confounders or risk factors. These covariates included: age, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Other), eGFR (mL/min/1.73 m^2), CD4 count (cells/mm^3), HIV viral load (copies/mL), diabetes status, treated

hypertension, smoking history (based on the presence of a tobacco use diagnosis, and categorized as never vs. ever smokers), and current use of medications, including ART, tenofovir disoproxil fumarate (TDF), insulin, metformin, and statins. Based on CNICS operational definitions, diabetes was defined as meeting at least one of the following criteria: 1) hemoglobin A1c ≥6.5%, 2) use of a diabetes-specific medication (e.g., insulin, sulfonylureas), or 3) use of a diabetes-related medication (a medication not exclusively used for diabetes (e.g., metformin)) subsequent to an earlier diabetes diagnosis.[33] Treated hypertension required both a hypertension diagnosis and a prescription for antihypertensive medication(s).

PS matching was performed using the nearest neighbor method without replacement and a caliper of 0.1.[34] Covariate balance was assessed using the standardized mean difference (SMD), with an SMD <10% indicating good balance. After matching, body mass index (BMI) and diabetes status remained imbalanced (SMD >10%). BMI was excluded from the PS model due to missing data (1.5% missingness), as including it would have reduced the number of matched individuals and compromised study power given the relatively small sample size. To address this post-matching imbalance, multiple imputation by chained equations (10 imputations) was performed for BMI, and outcome models were adjusted for BMI and diabetes, the two covariates that remained imbalanced after matching.

Time-to-event outcomes of eGFR decline were assessed using Cox proportional hazards models in the matched cohort with a robust variance estimator, adjusting for BMI and diabetes. For these analyses, the ITT follow-up definition was used. Results were reported as adjusted hazards ratios

(aHR) and 95% confidence intervals (CI). Schoenfeld residuals were used to assess the proportional hazards assumption.[35] A Kaplan-Meier analysis was performed to estimate the probabilities of ≥10% and ≥30% eGFR declines at 6 months, with Kaplan-Meier curves depicting the cumulative incidence of first observed decline over time.

For the eGFR change analysis, PWH were censored when they stopped treatment and were required to have at least one on-treatment eGFR measurement during the 6-month follow-up period. As a result, the number of PWH included in the on-treatment analyses was lower than in the ITT analyses. eGFR changes were assessed using linear mixed models with random intercepts and random slopes for time, adjusting for imbalanced covariates after matching. The on-treatment definition was used for these analyses, as ITT tends to yield more conservative estimates, potentially making SGLT2i treatment appear safer.

To visualize and estimate eGFR change trends beyond six months, we examined up to 24 months of follow-up and used locally weighted scatterplot smoothing (LOWESS) to model trajectories of eGFR for PWH initiating SGLT2i versus other antihyperglycemic classes. For contextual comparison, we also plotted eGFR trajectories derived from approximate mean changes reported in published randomized controlled trials among the general population (e.g., CREDENCE, DAPA-CKD, EMPA-REG). This nonparametric method fits smooth curves to localized data without assuming a specific functional form,[36] enabling us to capture nonlinear eGFR trajectories despite fewer observations after six months.

Additionally, to evaluate predictors of a ≥10% eGFR decline we used multivariable Poisson regression with robust variance, reporting adjusted risk ratios (aRRs) and 95% CIs. Analyses were conducted overall and stratified by treatment group (SGLT2i and other antihyperglycemic classes).

Subgroup analyses for time to ≥10% eGFR decline were performed based on age (≥60 vs. <60 years), sex (male vs. female), race/ethnicity (black vs. non-black), and baseline eGFR (≥60 vs. <60 mL/min/1.73m^2), but subgroup analyses for ≥30% decline were not conducted due to the small number of events. Effect modification was tested using an interaction term between treatment group and subgroup. A p-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 17 (StataCorp, College Station, TX).

To assess the robustness of our findings, we conducted three sensitivity analyses: (i) on-treatment analysis for time-to-event outcomes of ≥10% and ≥30% eGFR decline, censoring follow-up at treatment discontinuation or switching; (ii) ITT analysis for acute eGFR changes, assuming continuous exposure throughout the follow-up, regardless of discontinuation or switching; (iii) multivariable Cox regression analysis using the full cohort without applying PS matching, adjusting for baseline covariates (as another method to control for confounding).

4.5 Results

4.5.1 Baseline Patient Characteristics

We identified a total of 1,554 PWH who met inclusion criteria, including 299 new users of SGLT2i and 1,255 new users of other antihyperglycemic medications (585 GLP-1RA, 200 DPP-4 inhibitors, and 470 sulfonylureas; Supplemental Figure 4.1). After matching, 295 users of SGLT2i were

matched in a 1:1 ratio to 295 users of other antihyperglycemic medications, specifically 151 GLP-1RA users, 48 DPP-4i users, and 96 sulfonylurea users.

Prior to matching, there were significant differences between the groups (Table 4.1). SGLT2i users were older on average (56 vs. 53 years) and more likely to be male (81% vs. 74%). Those receiving SGLT2i also had a lower mean eGFR (71 vs. 83 mL/min/1.73m²) and included a higher proportion of PWH with moderate kidney impairment (eGFR 30–60 mL/min/1.73m²: 30% vs. 15%). After matching, baseline characteristics were generally well balanced between the two groups, including mean age (56 vs. 57 years), baseline eGFR (71 vs. 71 mL/min/1.73m²), and eGFR category ≥60-89 mL/min/1.73m² (44% vs 40%). Balance was poorer for diabetes status (69% vs. 74%) and BMI (31 vs. 33 kg/m²).

4.5.2 Follow-up eGFR Measurements

During the 6-month follow-up period, the median number of eGFR measurements was similar across groups, with a median of 2 (IQR: 1–4) for SGLT2i and 2 (IQR: 1–3) for other classes. The median time to the first eGFR measurement after medication initiation was shorter for SGLT2i: 69 days (IQR: 27–125) vs. 91 days (IQR: 44–134) for other classes.

4.5.3 Primary Outcomes

During 6 months follow-up, a total of 263 events of eGFR decline ≥10% and 72 events of eGFR decline ≥30% occurred among 590 PWH. The Kaplan-Meier cumulative incidence of ≥10% eGFR decline was higher among those initiating SGLT2i (58.2%, 95% CI: 52.4%–64.2%) compared to other antihyperglycemic classes (37.4%, 95% CI: 34.7%–40.4%), with SGLT2i use significantly associated with an increased risk of decline (aHR 1.79 [95% CI: 1.40–2.28]) (Figures 4.1 and 4.2). For ≥30% eGFR decline, 16.9% (95% CI: 12.9–22.1) of SGLT2i users experienced this outcome,

compared to 10.2% (95% CI: 7.1–14.4) of users of other antihyperglycemic classes, with SGLT2i use also associated with a higher risk compared to other classes (aHR 1.69 [95% CI: 1.05 – 2.73]) (Figures 4.1 and 4.2).

4.5.4 Secondary Outcomes

Change in eGFR over the 6-month follow-up period was assessed in on-treatment analysis, which included 278 on SGLT2i users and 265 on other antihyperglycemic classes. SGLT2i showed a greater absolute eGFR decline vs. other antihyperglycemic classes (−2.62 mL/min/1.73m² [95% CI: −7.90, 2.67] vs. +0.05 [95% CI: −3.00, 3.09]); however, the between-group difference was not statistically significant (p-interaction=0.3; Supplemental Table 4.1). Additional secondary outcomes, a decline of ≥20% and absolute declines of ≥10 and ≥5 mL/min/1.73m², further showed higher acute eGFR decline risk with SGLT2i versus other classes (Supplemental Figure 4.2).

Long-term eGFR trajectories, based on LOWESS-smoothed curves in the on-treatment population, revealed an acute decline in eGFR among SGLT2i users followed by partial recovery (Figure 4.3). The trajectories for the two groups crossed at approximately 14 months, after which the SGLT2i group experienced a slower rate of decline. However, only 149 SGLT2i users and 152 users of other classes had at least one eGFR measurement between 7 and 24 months, representing about 55% of the original cohort. Among these, the median number of eGFR measurements during this period was 4 (IQR 2–7 for SGLT2i; 2–9 for other classes). Exploratory multivariable analyses examining factors associated with ≥10% eGFR decline are presented in Supplemental Table 4.2.

4.5.5 Subgroup Analyses

Across all subgroups, SGLT2i was consistently associated with a higher risk of a ≥10% decline in eGFR compared to other antihyperglycemic classes. No statistically significant interactions were observed across subgroups (p-interaction > 0.05), indicating no evidence of effect modification (Supplemental Figure 4.3). Given the small subgroup sample sizes, these analyses were not powered to detect statistically significant differences and should be interpreted with caution.

4.5.6 Sensitivity Analyses

In the first sensitivity analysis, on-treatment results for ≥10% and ≥30% eGFR declines at 6 months were consistent with the main ITT analyses, also demonstrating higher risk among SGLT2i users versus other antihyperglycemic classes (Supplemental Table 4.3). The second sensitivity analysis, using ITT analysis for changes in eGFR at 6 months, demonstrated smaller mean eGFR declines in new users of SGLT2i compared to the on-treatment analyses, but the overall trend of greater eGFR decline among SGLT2i users remained consistent (Supplemental Table 4.4). This difference reflects the direct effects of SGLT2i in on-treatment analyses, while ITT likely estimate an attenuated effect by including those who discontinued or switched medications. The third sensitivity analysis, multivariable regression on the full cohort adjusted for baseline covariates, showed hazard ratios consistent with the propensity score-matched cohort (Supplemental Table 4.5).

4.6 Discussion

In our cohort study of PWH initiating antihyperglycemic medications, we found that acute eGFR decline within 6 months was more common following SGLT2i initiation compared to other

antihyperglycemic medications. However, the magnitude of the decline was, on average, small, non-clinically significant, and consistent with the eGFR dip observed in the general population.

A few studies have examined kidney function changes with SGLT2i in PWH, though data remain limited. Guiraud et al. examined 20 PWH receiving dapagliflozin or empagliflozin over a median 8.3-month follow-up and observed a small but significant median increase in serum creatinine of 17.5 µmol/L (~0.20 mg/dL), consistent with hemodynamic changes.[37] Similarly, Sise et al. studied 80 PWH receiving SGLT2i and found that 11.3% experienced AKI, a rate comparable to the 9.9% observed among PWH prescribed GLP-1s, suggesting that SGLT2i are generally safe in this population.[25] Together with our results, these findings suggest that initial eGFR changes with SGLT2i in PWH are generally modest and appear to be well tolerated.

Comparing our findings with studies of people without HIV is challenging given differences in patient populations, but such comparisons highlight both similarities and differences. In large trials and observational studies of the general population, ≥30% eGFR declines are relatively uncommon, ranging from 1 to 6%.[14,38] In our cohort, such declines were more frequent, 17% among PWH initiating SGLT2i and 10% among those on other antihyperglycemic classes. This higher incidence may reflect HIV-specific factors, including chronic inflammation, immune activation, [39–43] nephrotoxic effects of certain older ART medications (such as TDF),[44,45] or the impact of some ART agents, such as dolutegravir and cobicistat, which can inhibit tubular creatinine secretion and lead to mild increases in serum creatinine that do not represent true declines in kidney function.[46] Despite this, the magnitude of the average decline with SGLT2i was similar to that observed in HIV-negative populations. Moreover, the trajectory of eGFR over 24 months mirrored that of HIV-negative populations, with an initial decline followed by recovery

and stabilization. Reassuringly, these patterns are consistent with those seen in large trials, although the smaller sample size after 6 months in our cohort limits conclusions about long-term nephroprotection.

From a clinical perspective, these findings provide reassurance that the modest eGFR dip following SGLT2i initiation in PWH is not harmful and should not be interpreted as AKI.[47] In fact, studies in the general population suggest that SGLT2i reduce the risk of AKI while providing substantial cardiorenal benefits, even among patients who experience an initial dip.[14,38,48] Nevertheless, given that PWH may have increased susceptibility to clinically significant eGFR declines (≥30%), and although current guidelines do not recommend additional renal monitoring solely for the initiation of a SGLT2i,[23] clinicians should consider individualized monitoring based on the patient's overall risk profile. Recommendations for the general population, such as withholding SGLT2i if significant acute eGFR declines are observed and avoiding dose increases of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or diuretics before starting SGLT2i, would also be prudent for PWH.[22] In addition, these considerations are especially important for PWH, as many ART medications, particularly nucleoside reverse transcriptase inhibitors (NRTIs), are partially or completely renally eliminated,[49] potentially requiring dose adjustments of ART to avoid toxicity in case of very low eGFR.

4.6.1 Strengths and Limitations

Strengths of our study include leveraging real-world data from CNICS, a large, prospective cohort of PWH in routine clinical care, allowing our findings to be generalizable to diverse geographic and demographic populations of PWH.

The study has several limitations. Firstly, as an observational study, residual confounding is possible despite PS matching, which only accounts for measured variables. Important covariates such as ACE inhibitors, ARBs, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) were not included and may have introduced bias. Pre-matching differences between groups suggest potential channeling bias, with SGLT2i more often prescribed to PWH with more advanced kidney disease. While PS matching helped address baseline imbalances, some residual differences remained. Additionally, PWH on SGLT2i were more likely to undergo earlier eGFR measurements, potentially leading to differential surveillance bias and an overestimation of eGFR decline. Furthermore, due to variable timing of eGFR measurements, including some PWH with only a single follow-up, the Kaplan–Meier curves reflect the first observed decline and may not capture early, transient, or subsequent changes. This approach mirrors real-world clinical follow-up, where the timing of laboratory assessments varies across patients. Moreover, there is some potential for exposure misclassification, but if present is likely non-differential. Finally, these findings may only be generalizable to PWH in care. Additionally, because propensity score matching estimates the average treatment effect among the treated, the results should be interpreted as applicable to individuals initiating SGLT2 inhibitors and their matched comparators, and may not be generalizable to the broader population of eligible patients.

4.7 Conclusion

Given the increased risk of kidney disease in PWH, evaluating new, effective therapies like SGLT2i is essential. We found that early, small eGFR declines were more common among PWH initiating SGLT2i, consistent with class effects observed in the general population. However, clinically significant eGFR declines of ≥30% were more frequent in both SGLT2i and other

antihyperglycemic users compared to what is typically seen in HIV-negative populations, suggesting that HIV-related factors may increase susceptibility. While these findings are reassuring, clinicians should remain vigilant for early eGFR declines following SGLT2i initiation and consider individualized monitoring. As CKD continues to emerge as a major comorbidity, further long-term studies are needed to assess whether SGLT2i offer similar nephroprotective benefits in PWH.

4.8 Tables and Figures

Table 4.1. Baseline Characteristics of People with HIV (PWH) Initiating SGLT2 Inhibitors vs. Other Antihyperglycemic Classes, Before and After Propensity Score (PS) Matching

	Before PS matching		After PS matching		
Characteristic	**SGLT2 Inhibitors (n, %)**	**Other classes (n, %)**	**SGLT2 Inhibitors (n, %)**	**Other classes [a] (n, %)**	**SMD [b] (%)**
N	299	1255	295	295	
Age, years (Mean, SD)	56 (10)	53 (10)	56 (10)	57 (10)	5.5
Sex					
Male	241 (81)	932 (74)	237 (80)	245 (83)	7.0
Female	58 (19)	323 (26)	58 (20)	50 (17)	
Race					
Non-Hispanic White	111 (37)	431 (34)	111 (38)	106 (36)	4.4
Non-Hispanic Black	147 (49)	575 (46)	143 (49)	147 (50)	
Hispanic	27 (9)	194 (16)	27 (9)	29 (10)	
Other	14 (5)	55 (4)	14 (5)	13 (4)	
eGFR, mL/min/1.73m² (Mean, SD)	69 (23)	83 (23)	71 (23)	71 (23)	1.7
eGFR categories					
≥ 90	70 (23)	537 (43)	70 (24)	71 (24)	8.3
≥ 60 to <90	129 (43)	500 (40)	129 (44)	119 (40)	
≥ 30 to <60	91 (30)	197 (16)	87 (30)	97 (33)	
≥ 15 to <30	9 (3)	21 (2)	9 (3)	8 (3)	
Diabetes	203 (68)	1034 (82)	203 (69)	218 (74)	11.3
Treated Hypertension	227 (76)	845 (67)	223 (76)	230 (78)	5.6
CD4 Count, cells/mL (Mean, SD)	676 (375)	724 (386)	675 (375)	665 (347)	2.7
VL <200, copies/mL	273 (91)	1157 (92)	271 (92)	274 (93)	3.8
BMI, kg/m² (Mean, SD)	31 (8)	34 (8)	31 (8)	33 (7)	24.0
Concomitant Baseline Medications					
ART	291 (97)	1217 (97)	287 (97)	286 (97)	2.0
TDF	44 (15)	302 (24)	44 (15)	42 (14)	1.9
DTG	119 (40)	430 (34)	117 (40)	108 (37)	6.3
RPV	28 (9)	116 (12)	28 (10)	30 (10)	2.2
COBI	29 (10)	152 (12)	29 (10)	37 (13)	8.6
Insulin	63 (21)	235 (19)	63 (21)	67 (23)	3.3
Metformin	115 (38)	669 (53)	112 (38)	124 (42)	8.3
Statins	206 (69)	688 (55)	202 (69)	204 (69)	1.5
Ever Smoker	141 (47)	451 (36)	138 (47)	130 (44)	5.5

Note: a Others group consists of GLP-1 RA (n=151), DPP-4 inhibitors (n=48), and sulfonylureas (n=96). b SMD <10% indicates good balance between groups.

Abbreviations: *SMD: Standardized mean difference, SGLT2i: Sodium-glucose cotransporter-2 inhibitor, eGFR: Estimated glomerular filtration rate, VL: Viral load, BMI: Body mass index, ART: Antiretroviral therapy, TDF: Tenofovir disoproxil fumarate, DTG: Dolutegravir; RPV: Rilpivirine; COBI: Cobicistat.*

Figure 4.1. Adjusted hazard ratios (aHRs) for ≥10% and ≥30% estimated glomerular filtration rate (eGFR) decline within 6 months of sodium–glucose cotransporter-2 inhibitor (SGLT2i) versus other antihyperglycemic class initiation among people with HIV (PWH) in a propensity score–matched cohort (N=590).

*Models were adjusted for diabetes status and baseline BMI due to residual imbalance after matching (standardized mean difference >10%).

Abbreviations: *SGLT2i, sodium–glucose cotransporter-2 inhibitor; eGFR, estimated glomerular filtration rate; aHR, adjusted hazard ratio*

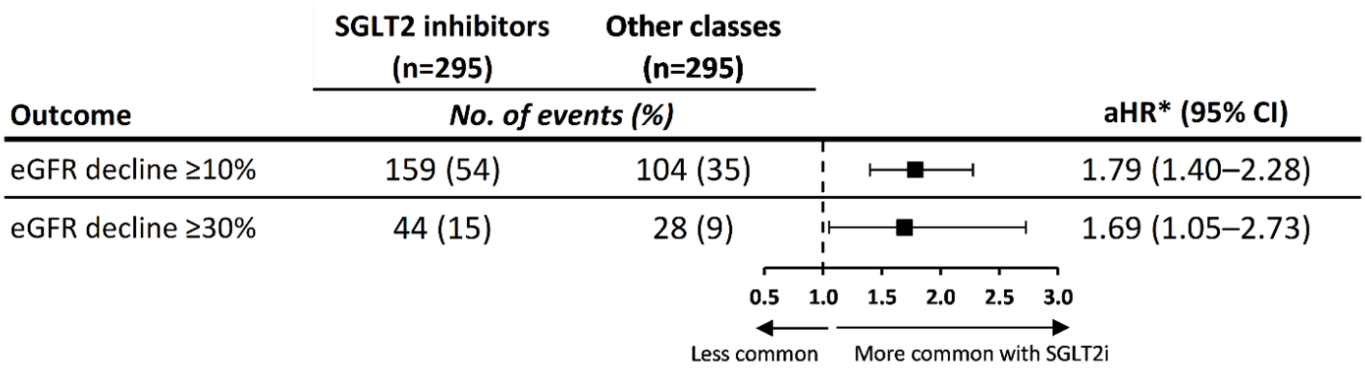


Figure 4.2. Kaplan-Meier curves for cumulative incidences of ≥10% (Panel A) and ≥30% (Panel B) eGFR decline within 6 Months of SGLT2 Inhibitors vs. other antihyperglycemic classes initiation in propensity score-matched cohort of PWH (N=590).

Abbreviations: *SGLT2i, sodium–glucose cotransporter-2 inhibitor; eGFR, estimated glomerular filtration rate*

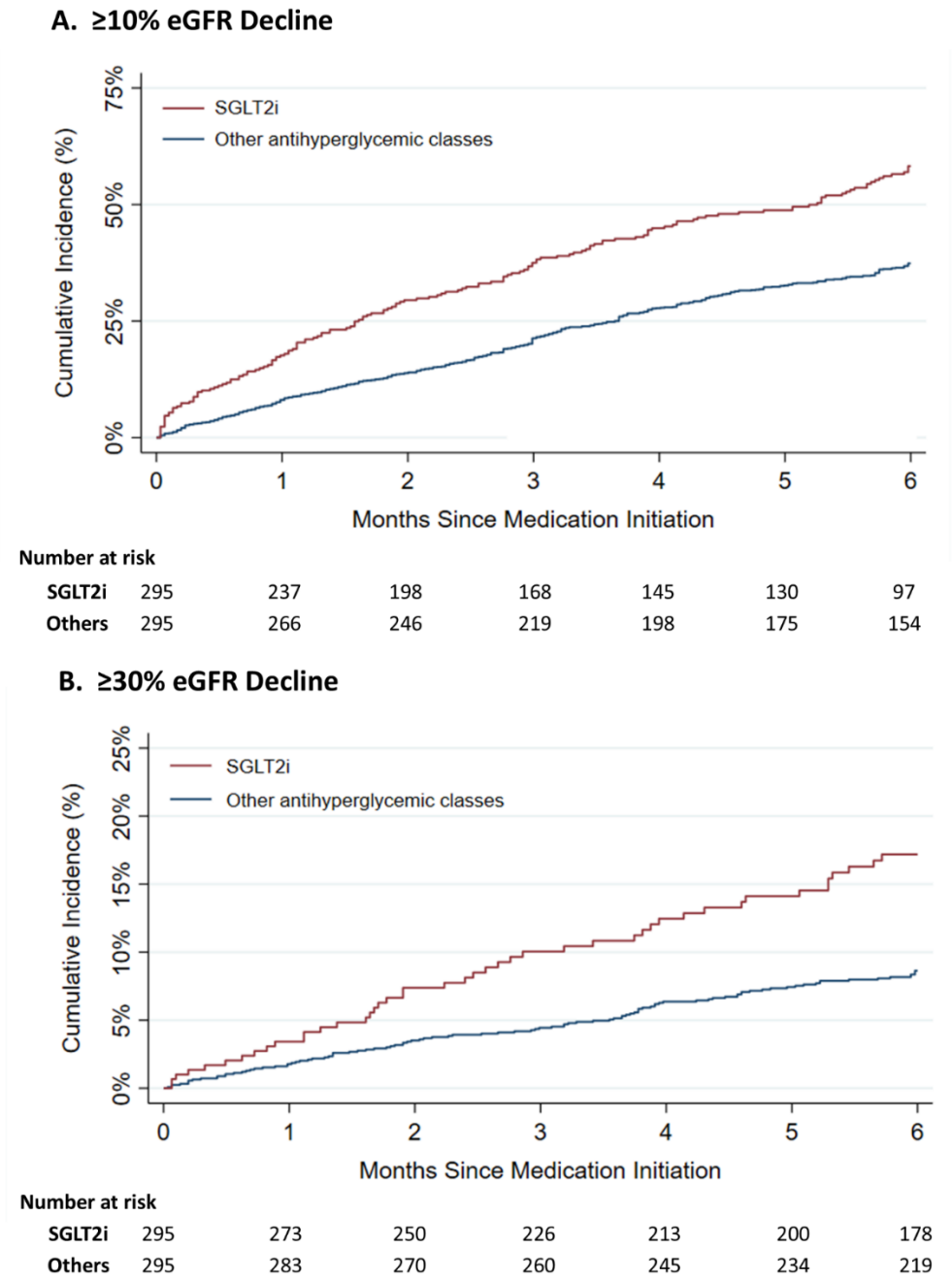
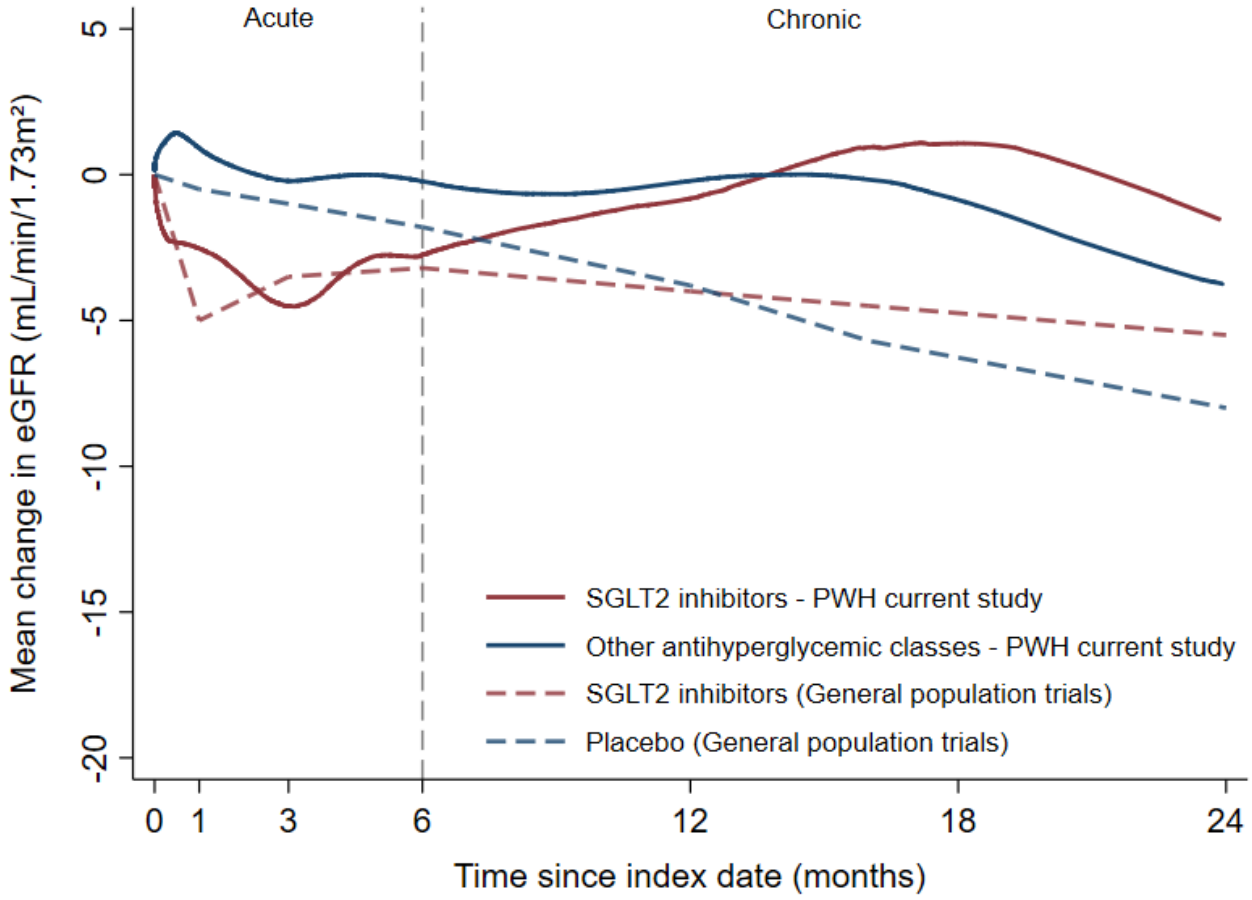


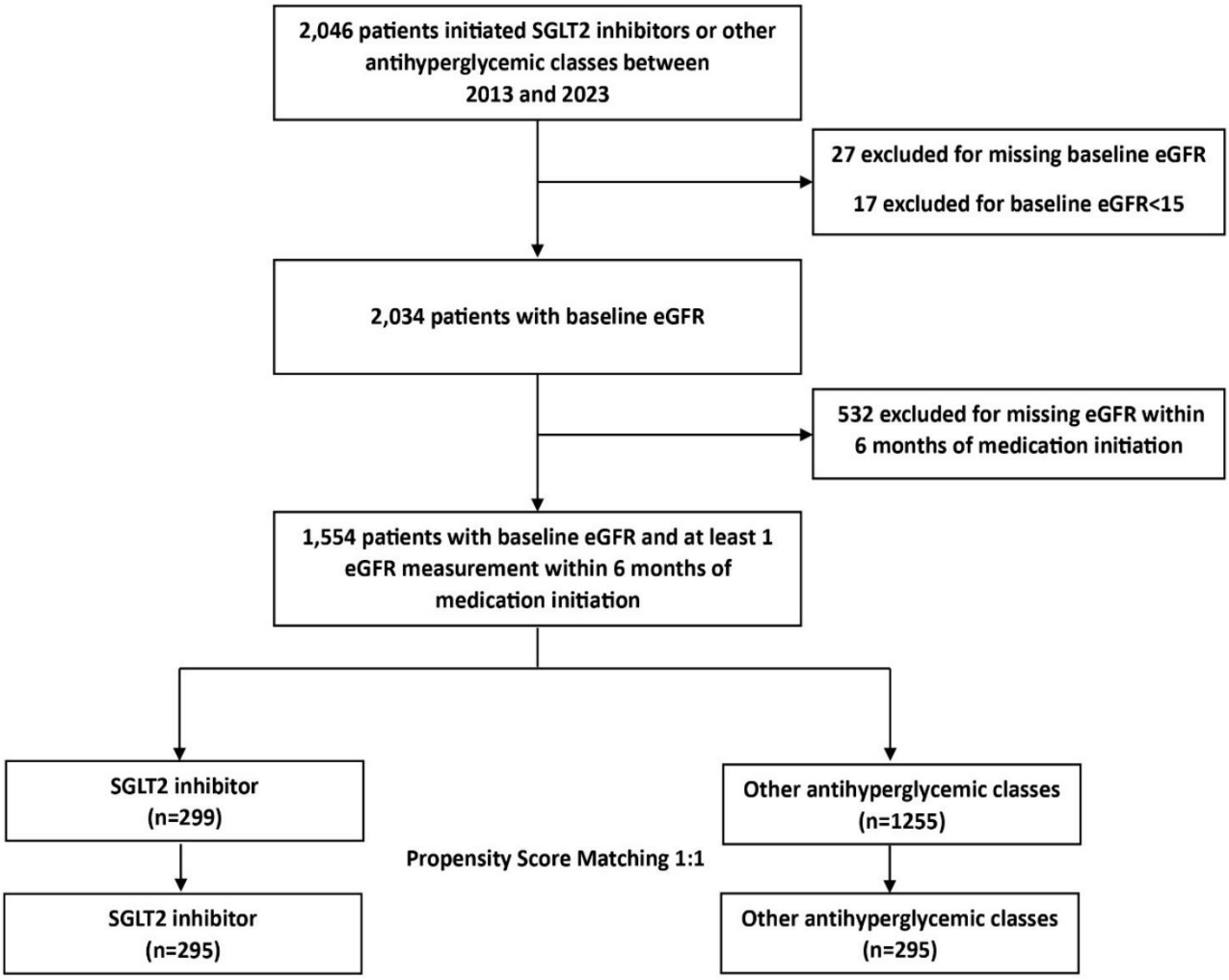
Figure 4.3. Change in eGFR over time following initiation of SGLT2i versus other antihyperglycemic classes among PWH (on-treatment, N = 543), with reference to general population clinical trial data. LOWESS-smoothed eGFR trajectories over 24 months for PWH initiating SGLT2i (red line) or other antihyperglycemic classes (blue line) are overlaid with dashed lines representing approximate mean changes in eGFR reported in randomized controlled trials (RCTs) among the general population (e.g. CREDENCE, DAPA-CKD, and EMPA-REG). The eGFR trajectory in PWH follows a similar pattern to that observed in large, RCTs of SGLT2i from the general population, with an initial decline during the acute phase (0–6 months) after SGLT2i initiation, followed by partial recovery and stabilization with a crossover around 12–14 months, after which SGLT2i users exhibit a slower rate of eGFR decline compared to controls. LOWESS plots illustrate the trend in eGFR changes over time and are for descriptive purposes only.

Abbreviations: *SGLT2i, sodium–glucose cotransporter-2 inhibitor; eGFR, estimated glomerular filtration rate; PWH, people with HIV; RCT, randomized controlled trial; LOWESS, locally weighted scatterplot smoothing.*



4.9 Supplementary Tables and Figures

Supplmental Figure 4.1. Flowchart of Study Cohort Selection and Propensity Score Matching



Supplemental Table 4.1. Change in Mean eGFR at 6 Months (On-Treatment Analysis; N=543)

Outcome	SGLT2 inhibitors (n=278)	Other classes (n=265)	Interaction p-value
Mean change in eGFR mL/min/1.73m² (95% CI)	-2.62 (-7.90, 2.67)	0.05 (-3.00, 3.09)	0.3

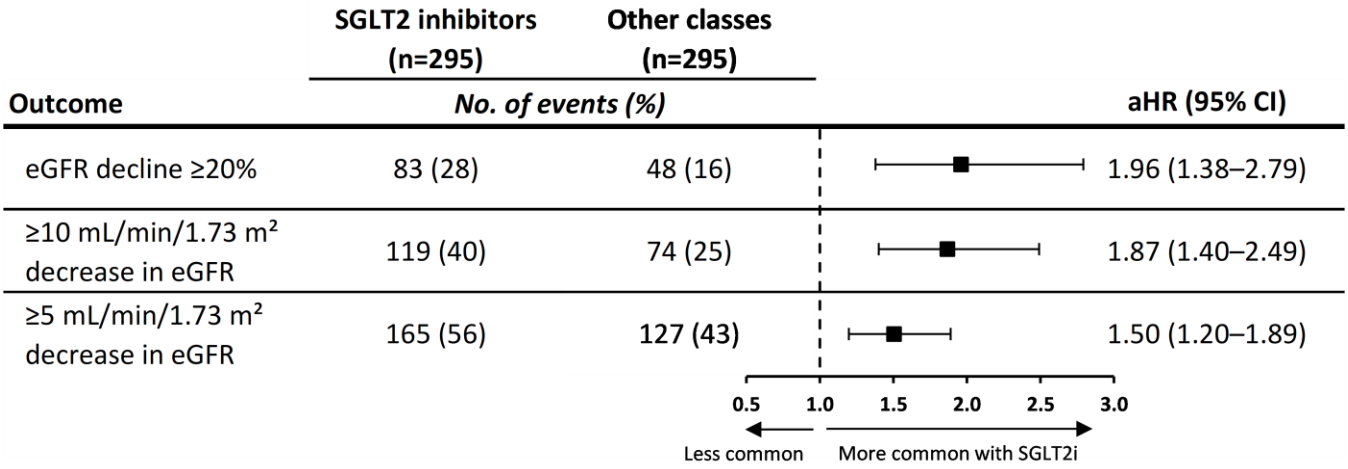
Adjusted for diabetes status and BMI at baseline

Supplemental Table 4.2. Multivariable Poisson Regression of Factors Associated with ≥10% eGFR Decline Among PWH, Overall and by Treatment Group

Variable	All PWH (n=590) aRR (95% CI)	SGLT2i (n=295) aRR (95% CI)	Other (n=295) aRR (95% CI)
Age (per 10y)	0.99 (0.89–1.10)	1.04 (0.92–1.17)	0.90 (0.73–1.09)
Female (ref: Male)	0.90 (0.70–1.16)	0.71 (0.52–0.98)	1.03 (0.69–1.54)
Black (ref: White)	1.01 (0.83–1.24)	1.25 (0.99–1.59)	0.78 (0.55–1.10)
Hispanic (ref: White)	1.07 (0.79–1.46)	1.28 (0.91–1.80)	0.87 (0.49–1.54)
Other race/ethnicity (ref: White)	0.67 (0.37–1.23)	0.60 (0.27–1.33)	0.76 (0.32–1.81)
Baseline eGFR (per 10 mL/min/1.73m²)	1.03 (0.99–1.08)	1.02 (0.97–1.07)	1.06 (0.98–1.15)
CD4 (per 100 cells/mL)	0.98 (0.95–1.01)	0.98 (0.95–1.01)	0.97 (0.92–1.02)
VL <200 (ref: ≥200 copies/mL)	0.88 (0.62–1.25)	0.81 (0.52–1.25)	0.98 (0.53–1.82)
Hypertension (ref: no hypertension)	1.14 (0.89–1.47)	1.01 (0.78–1.31)	1.70 (1.02–2.86)
Diabetes (ref: no diabetes)	1.08 (0.85–1.36)	0.95 (0.73–1.23)	1.31 (0.84–2.05)
Baseline BMI (per 1 kg/m²)	1.00 (0.98–1.01)	1.01 (1.00–1.03)	0.99 (0.96–1.01)
Ever Smoking (ref: never)	1.14 (0.95–1.37)	1.00 (0.80–1.25)	1.32 (0.97–1.80)
Medications			
TDF (ref: no TDF)	0.87 (0.66–1.13)	1.07 (0.80–1.45)	0.63 (0.37–1.05)
Statin (ref: no statin)	0.84 (0.69–1.02)	0.88 (0.70–1.10)	0.89 (0.63–1.24)
Insulin (ref: no insulin)	1.26 (1.02–1.56)	1.07 (0.81–1.41)	1.51 (1.06–2.16)
Metformin (ref: no metformin)	0.77 (0.62–0.95)	0.76 (0.58–0.996)	0.77 (0.55–1.07)
Diuretic (ref: no diuretic)	1.29 (1.07–1.56)	1.18 (0.93–1.51)	1.10 (0.78–1.55)
ACE inhibitor (ref: no ACE)	1.25 (1.02–1.55)	1.21 (0.95–1.55)	1.25 (0.85–1.83)
ARB (ref: no ARB)	1.08 (0.84–1.38)	1.08 (0.81–1.42)	0.96 (0.60–1.54)

Abbreviations: *aRR, adjusted risk ratio; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (kg/m²); eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); PWH, people with HIV; SGLT2i, sodium–glucose cotransporter-2 inhibitor; TDF, tenofovir disoproxil fumarate; VL, HIV viral load*

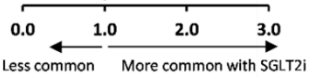
Supplemental Figure 4.2. Hazard Ratios for Secondary Time-to-Event Outcomes within 6 Months of SGLT2 Inhibitor vs. Other Antihyperglycemic Initiation in Propensity Score-Matched Cohort of People with HIV (N=590)



Adjusted for diabetes status and BMI at baseline

Supplemental Figure 4.3. Subgroup analyses for ≥10% eGFR decline by age, sex, race/ethnicity, and baseline eGFR

Subgroup	SGLT2 inhibitors (n=295) *No. of events/Total (%)*	Other classes (n=295) *No. of events/Total (%)*	aHR (95%CI)	Interaction p-value
Age (years)				
<60	98/182 (53.9%)	63/178 (35.4%)	1.76 (1.28–2.42)	0.86
≥60	61/113 (54.0%)	41/117 (35.0%)	1.84 (1.26–2.69)	
Sex				
Male	133/237 (56.1%)	87/245 (35.5%)	1.93 (1.47–2.54)	0.20
Female	26/58 (44.8%)	17/50 (34.0%)	1.28 (0.73–2.25)	
Race				
Black	83/143 (58.0%)	49/147 (33.3%)	2.04 (1.43–2.92)	0.29
Non-black	76/152 (50.0%)	55/148 (37.1%)	1.56 (1.12–2.18)	
eGFR (mL/min/1.73m²)				
≥60	108/199 (54.3%)	68/190 (35.8%)	1.79 (1.33–2.41)	0.97
<60	51/96 (53.1%)	36/105 (34.3%)	1.77 (1.15–2.73)	



Models were adjusted for diabetes status and baseline BMI due to residual imbalance after matching (standardized mean difference >10%). Adjusted hazard ratios are shown, and interaction p-values assess effect modification across subgroups.

Abbreviations: *SGLT2i, sodium–glucose cotransporter-2 inhibitor; eGFR, estimated glomerular filtration rate; aHR, adjusted hazard ratio*

Supplemental Table 4.3. On-Treatment Analysis for Primary and Secondary Time-to-Event Outcomes (N=543)

Outcome	SGLT2 inhibitors (n=278)	Other classes (n=265)	aHR* (95% CI)
	no. of events (%)	*no. of events (%)*	
Primary			
≥10% decline in eGFR	149 (53.6%)	89 (33.6%)	1.79 (1.38–2.31)
≥30% decline in eGFR	40 (14.4%)	22 (8.3%)	1.79 (1.06–3.00)
Secondary			
≥20% decline in eGFR	80 (28.8%)	39 (14.7%)	2.13 (1.46–3.12)
≥ 10 ml/min decrease in eGFR	110 (39.6%)	63 (23.8%)	1.84 (1.35–2.50)
≥ 5 ml/min decrease in eGFR	154 (55.4%)	112 (42.3%)	1.47 (1.16–1.86)

*Adjusted for diabetes status and BMI at baseline

Supplemental Table 4.4. Intention-to-Treat (ITT) Analysis of eGFR Change at 6 Months (N=590)

Outcome	SGLT2 inhibitors (n=295)	Other classes (n=295)	Interaction p-value
Mean Change in eGFR mL/min/1.73 m² (95% CI)	-1.59 (-6.40, 3.23)	2.36 (-0.92, 5.65)	0.1

Adjusted for diabetes status and BMI at baseline

Supplemental Table 4.5. Multivariable Regression-Adjusted Hazard Ratios for Primary and Secondary Time-to-Event Outcomes in the Full Cohort Comparing SGLT2 Inhibitors with Other Antihyperglycemic Classes (N=1554)

Outcome	SGLT2 inhibitors (n=299)	Other classes (n=1255)	aHR* (95% CI)
	no. of events (%)	*no. of events (%)*	
Primary			
≥10% decline in eGFR	162 (54.2%)	442 (35.2%)	1.74 (1.43–2.12)
≥30% decline in eGFR	45 (15.1%)	100 (8.0%)	1.76 (1.19–2.61)
Secondary			
≥20% decline in eGFR	85 (28.4%)	196 (15.6%)	1.95 (1.48–2.57)
≥ 10 ml/min decrease in eGFR	120 (40.1%)	370 (29.5%)	1.77 (1.42–2.21)
≥ 5 ml/min decrease in eGFR	168 (56.2%)	576 (45.9%)	1.43 (1.19–1.73)

*Adjusted for age, sex, race/ethnicity, baseline BMI, baseline eGFR, CD4 count, HIV viral load, diabetes status, treated hypertension, use of tenofovir disoproxil fumarate (TDF), statin use, insulin use, metformin use, and smoking history.

Acknowledgements: The authors acknowledge all CNICS participants and study personnel for their essential contributions to this work.

4.10 Contributions of Authors:

- **Study and analytic design:** L.H., R.M.N., H.M.C., S.E., J.A.C.D.
- **Statistical analysis:** L.H., R.M.N.
- **Manuscript writing:** L.H.
- **Manuscript revision:** All authors contributed to critical revisions and approved the final version.

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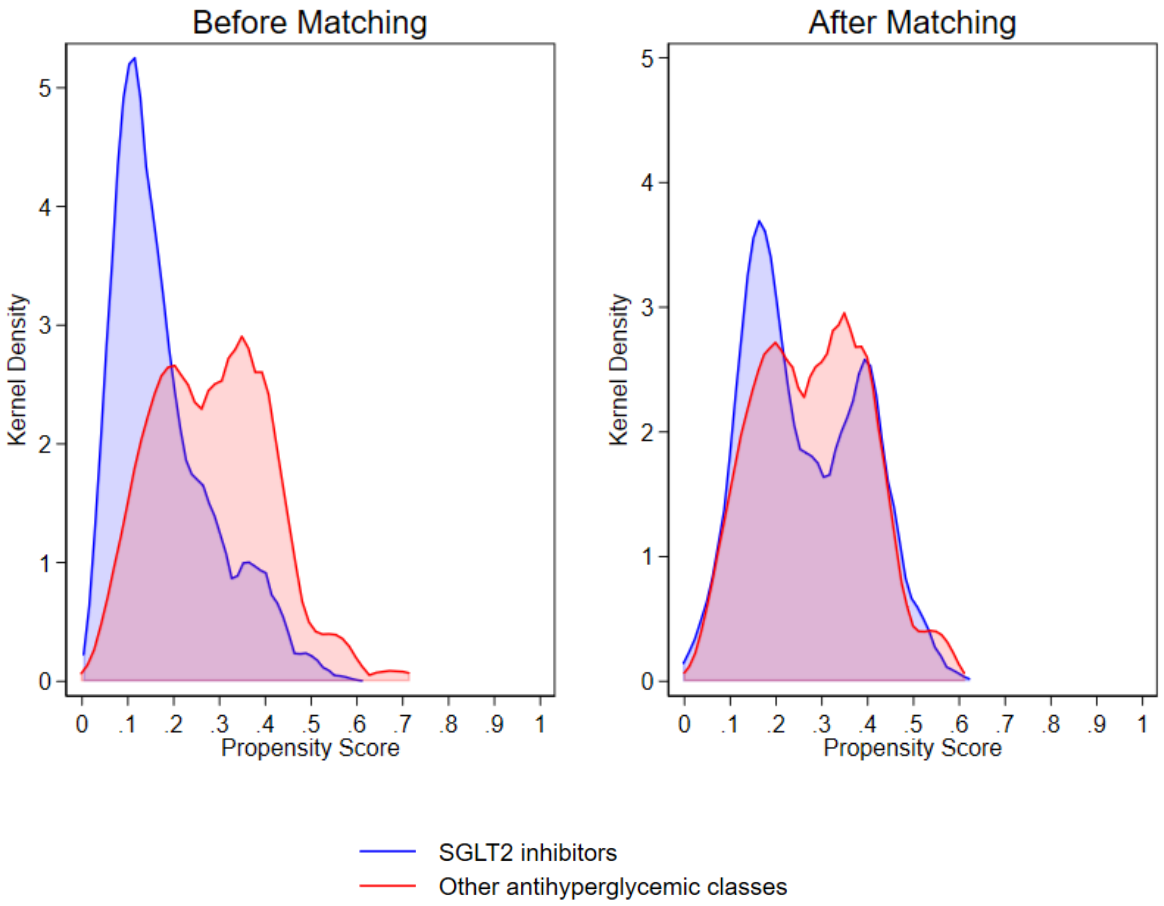
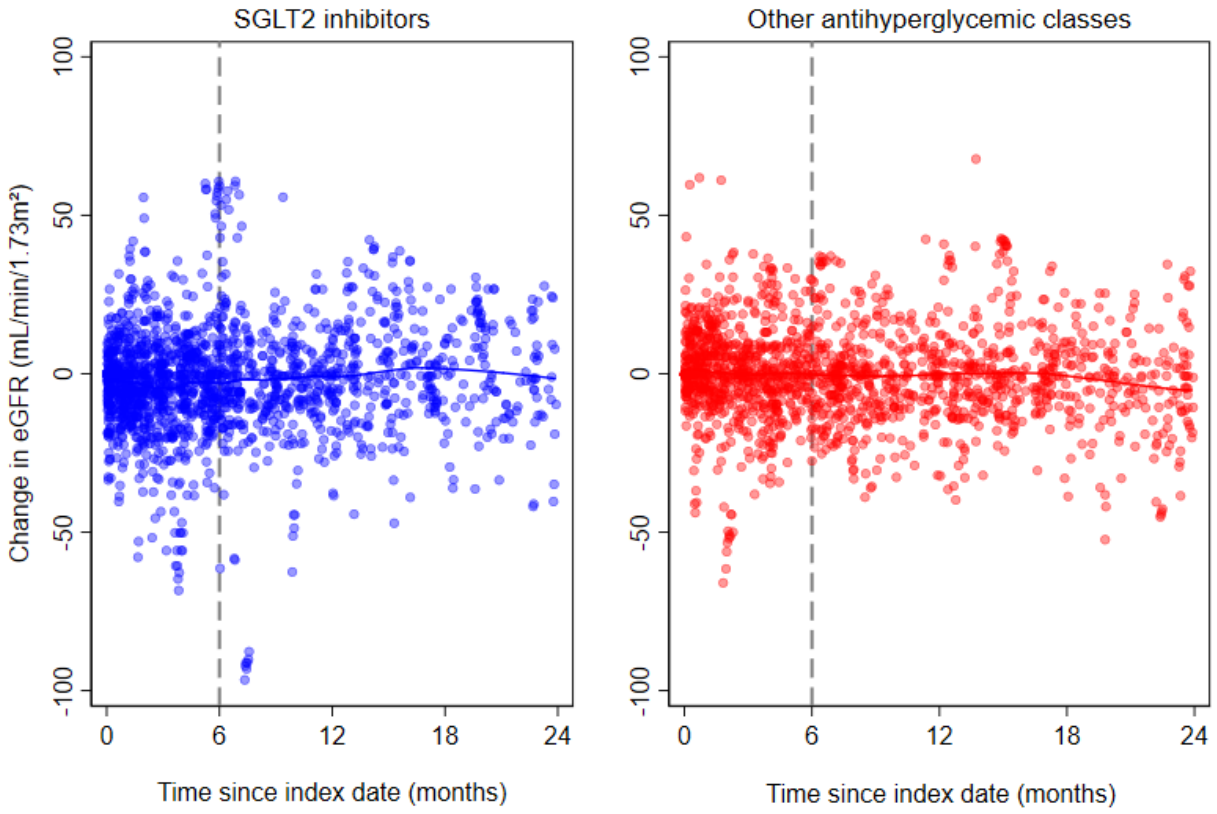
4.12 Additional Results (Not Included in the Submitted Manuscript)

In addition to the results reported in the manuscript and its supplementary materials, the following analyses were conducted to complement the findings presented in this chapter. These results were not included in the submitted paper but are presented here to provide additional context and depth for the thesis. Unless otherwise specified, the data were derived from the same study population and analytic framework described earlier in this chapter.

Additional Figure 4.1. Propensity Score Distributions Before and After Matching



Additional Figure 4.2. Scatter and LOWESS plots showing changes in eGFR (mL/min/1.73m²) from baseline over 24 months among PWH treated with SGLT2 inhibitors (left) and other antihyperglycemic classes (right). Each point represents an individual measurement; LOWESS smoothing lines illustrate average trajectories. The vertical dashed line indicates 6 months post-index "acute phase".



Chapter 5. Safety of Semaglutide on Depressive Symptoms Among People with HIV in Routine Clinical Care

5.1 Overview

This manuscript addresses the final objective of the thesis. The first two manuscripts established the metabolic benefits of glucagon-like peptide-1 receptor agonists (GLP-1RAs), particularly semaglutide, among people with HIV (PWH). However, as semaglutide use has rapidly increased for the management of diabetes and obesity, emerging reports have raised concerns regarding its psychiatric safety, including possible associations with depression and suicidality. Depression is the most common mental health comorbidity among PWH and is a major barrier to engagement in care, adherence to antiretroviral therapy (ART), and the achievement of optimal health outcomes. Therefore, it is critical to examine the psychiatric safety of semaglutide in this unique population.

This study aimed to determine whether semaglutide use is associated with worsening depressive symptoms among PWH receiving routine clinical care. Using data from a large, multicenter U.S. cohort, we examined changes in depressive symptoms, as measured by the Patient Health Questionnaire-9 (PHQ-9), before and after semaglutide initiation. Among 354 PWH who were new users of semaglutide, treatment initiation was not associated with a worsening of PHQ-9 scores. These findings provide initial evidence supporting the psychiatric safety of semaglutide among PWH.

Manuscript status: Manuscript under review

Safety of Semaglutide on Depressive Symptoms Among People with HIV in Routine Clinical Care

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5.2 Abstract

Background: Semaglutide, widely used for diabetes and obesity, has raised concerns about neuropsychiatric risks, including depression and suicidality. Given the high burden of depression among people with HIV (PWH), we assessed whether semaglutide initiation worsens depressive symptoms.

Methods: We conducted a within-person pre–post study of PWH initiating semaglutide at nine Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites between April 2018 and October 2024. Depressive symptoms were measured using the Patient Health Questionnaire–9 (PHQ-9) collected during routine care before and after semaglutide initiation. We estimated changes in PHQ-9 scores after semaglutide initiation using linear mixed models, overall and stratified by baseline depression severity (0–4 no/minimal, 5–9 mild, 10–14 moderate, and ≥15 moderately-severe to severe), body mass index (BMI), diabetes, and antidepressant use.

Results: Among 354 PWH (mean age 54; 77% male; 38% non-Hispanic White; 78% obesity; 60% diabetes), baseline PHQ-9 scores were 0–4 in 53%, 5–9 in 28%, 10–14 in 10%, and ≥15 in 9%. Semaglutide was not associated with overall changes in depressive symptoms (ΔPHQ-9 −0.1 [95% CI −0.7, 0.5]). Scores increased slightly in those with no/minimal baseline depression (+1.2 [95% CI 0.5, 1.8]), were stable in mild/moderate depression, and decreased in moderately-severe to severe depression (−4.7 [95% CI −7.3, −2.2]). No worsening was observed across BMI, diabetes, or antidepressant subgroups.

Conclusion: Semaglutide initiation was not associated with worsening depressive symptoms among PWH in care. While individual responses may vary, these findings add to evidence on semaglutide safety regarding mood in a high-risk population.

5.3 Introduction

Depression is the most common psychiatric condition among people with HIV (PWH), affecting an estimated 20–40%, roughly three times higher than in the general population[1–4] Depression is associated with lower antiretroviral therapy adherence, reduced HIV viral suppression, and increased morbidity and mortality in PWH.[5,6] Obesity and type 2 diabetes are also increasingly common among PWH in the modern era,[7,8] leading to growing use of medications such as semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), that have demonstrated efficacy for weight loss and glycemic control.[9]

Concerns have emerged regarding the neuropsychiatric safety of GLP-1RA, following early pharmacovigilance reports suggesting possible increases in depression and suicidal behavior.[10,11] However evidence is mixed, with some studies indicating potential adverse effects on mood and more recent large studies suggesting neutral or potentially beneficial effects on depression and suicidality.[12–19] Regulatory agencies, including the U.S. Food and Drug Administration and European Medicines Agency, have concluded that current evidence does not support a causal link.[20,21]

Evidence on the mental health safety of semaglutide in PWH, who experience high rates of depression and unique psychosocial vulnerabilities is limited. Most prior studies have been conducted in the general population and in participants without pre-existing depression. Given the increasing real-world use of semaglutide in this population, understanding its safety regarding depressive symptoms is essential. Therefore, we examined changes in depressive symptoms,

measured by the Patient Health Questionnaire-9 (PHQ-9), following initiation of semaglutide in a large US cohort of PWH in care.

5.4 Methods

5.4.1 Study Design and Population

We conducted a within-person, pre-post quasi-experimental study using data from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort. CNICS is a multicenter, prospective clinical cohort of over 50,000 adults with HIV receiving routine care across academic centers in the US. It integrates detailed clinical data from electronic medical records and institutional data systems, including diagnoses, medication prescriptions, laboratory results, and demographics. Participants also complete patient-reported outcome (PRO) assessments, including the PHQ-9, as part of routine clinical care approximately every six months. Sites received local institutional review board approval to participate in CNICS.

We included PWH who newly initiated semaglutide, the most widely prescribed GLP-1RA in CNICS, between April 2018 and October 2024 and had ≥1 PHQ-9 assessment before and ≥1 after initiation. Baseline was defined as date of semaglutide initiation, which served as the index date.

5.4.2 Exposure Assessment

New semaglutide treatment was defined as first-ever prescription, including subcutaneous or oral formulations, at any dose and for any indication (i.e., diabetes or obesity). Medication data in CNICS are collected from electronic medical records, provider order entry, and/or pharmacy databases.

5.4.3 Outcome Measures

The primary outcome was change in depressive symptoms following semaglutide initiation, measured using the PHQ-9, a validated self-reported outcome routinely administered as part of clinical care.[22] PHQ-9 assesses nine depressive symptoms over the past two weeks with each item scored from 0 (“not at all”) to 3 (“nearly every day”), for a total score ranging from 0 to 27. Higher scores indicate greater symptom severity. PHQ-9 scores are commonly categorized as no/minimal (0–4), mild (5–9), moderate (10–14), moderately-severe (15–19), and severe (20–27). A score of ≥10 demonstrates 88% sensitivity and specificity for detecting major depressive disorder,[22] and a 5-point reduction is considered clinically meaningful.[23]

Baseline PHQ-9 score was defined as the assessment closest to, but preceding, semaglutide initiation. All PHQ-9 assessments within four years prior to semaglutide initiation were included to improve estimation of the cohort’s pre-treatment symptom trajectory, and all assessments conducted after initiation while on semaglutide were also included.

5.4.4 Covariates

Baseline covariates, all assessed prior to semaglutide initiation, included: age, sex, race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and Other); diabetes defined according to CNICS operational criteria as having one or more of the following: hemoglobin A1c ≥6.5%, use of diabetes-specific medications (e.g., insulin, sulfonylureas), or use of diabetes-related medication (e.g., metformin) combined with a diabetes diagnosis;[24] hypertension defined as having both a documented diagnosis and active treatment with antihypertensive medication(s); body mass index (BMI) calculated as weight in kilograms divided by height in

meters squared (kg/m²) using the most recent measurement available prior to semaglutide initiation; and antidepressant use, defined as an active prescription at the time of semaglutide initiation, for commonly used antidepressant classes, including selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other antidepressants such as bupropion and mirtazapine.

5.4.5 Statistical Analysis

Baseline characteristics were summarized using means and standard deviations (SD) for continuous variables and frequencies with percentages for categorical variables.

The primary analysis estimated average within-person changes in PHQ-9 scores following semaglutide initiation using linear mixed models (LMMs) incorporating all pre- and post-treatment PHQ-9 assessments in an on-treatment analysis, with follow-up continuing until semaglutide discontinuation or the last PHQ-9 measurement through October 2024. Models were adjusted for age, sex, race/ethnicity, and continuous time relative to treatment initiation. LMMs account for correlations among repeated measures, handle irregularly timed data, and use all available PHQ-9 assessments.

We examined the primary outcome, changes in PHQ-9 scores, in the overall cohort and across subgroups defined by baseline depression severity based on PHQ-9 scores (no/minimal 0–4, mild 5–9, moderate 10–14, and moderately-severe to severe ≥15), as well as across clinical subgroups according to obesity (BMI <30, 30–34.9, ≥35 kg/m²), diabetes status (yes vs no), antidepressant use (yes vs no), and final semaglutide dose, categorized as low-to-moderate (injectable 0.25, 0.5, or 1 mg; oral 3 or 7 mg) or high (injectable 1.7, 2, or 2.4 mg; oral 14 mg). Separate stratified

models were used for these subgroups, and no formal interaction tests were conducted due to limited sample size in most strata. As an exploratory analysis, we evaluated whether changes in depressive symptoms following semaglutide initiation differed across clinical subgroups nested within baseline severity strata (PHQ-9 0–4, 5–9, and ≥10).

We conducted several sensitivity analyses. First, an intention-to-treat (ITT) analysis included all post-initiation PHQ-9 measurements, regardless of semaglutide discontinuation, whereas the primary on-treatment analysis ended follow-up at discontinuation. Second, recognizing that the PHQ-9 reflects symptoms over the preceding two weeks, we repeated the primary analysis excluding PHQ-9 assessments collected within the first month following semaglutide initiation, introducing a 1-month lag. Third, analysis was restricted to PWH with ≥1 PHQ-9 measurement ≤12 months pre-initiation, with the measurement closest to initiation defined as baseline, and all pre- and post-treatment measurements included. Fourth, pre-treatment measurements were truncated to only those within 12 months prior to initiation, while retaining all post-treatment measurements (sensitivity analyses 1–4, Figure 5.1). Fifth, pre-initiation trends in PHQ-9 scores were analyzed to assess stability of depressive symptoms before semaglutide initiation.

Fifth, pre-initiation trends in PHQ-9 scores were analyzed to assess stability of depressive symptoms before semaglutide initiation. Sixth, to further evaluate potential regression to the mean and floor effects at the lower end of the PHQ-9 scale we stratified PWH with baseline PHQ-9 scores of 0–4 into 0–1 and 2–4 categories. Seventh, to assess whether changes in depressive symptoms were influenced by concurrent changes in antidepressant therapy, we conducted two sensitivity analyses restricted to PWH with stable antidepressant medication use. Stable antidepressant medication use was defined as no initiation, discontinuation, medication switch,

or dose adjustment. The first analysis restricted the cohort to PWH with stable antidepressant use between semaglutide initiation and the first post-initiation PHQ-9 assessment. The second analysis further restricted the cohort to PWH with stable antidepressant use during the entire follow-up period.

Finally, as the largest improvements in PHQ-9 scores were observed among PWH with baseline scores ≥15, we conducted a matched analysis restricted to this subgroup to assess whether these changes reflected true treatment effects rather than solely regression to the mean. Within this subgroup (baseline PHQ-9 ≥15), PWH who initiated semaglutide during the study period ("users") were matched to PWH who never initiated semaglutide ("non-users"), with candidate non-users also required to have baseline PHQ-9 scores ≥15 to ensure all comparisons were within the severe symptom group. For semaglutide users, the index date was defined as the date of their first prescription; for non-users, the index date was assigned as the date of their first PHQ-9 assessment occurring on or after September 20, 2019, one year prior to the first semaglutide initiation in the cohort. This ensured temporal alignment of follow-up between groups and minimized immortal time bias. Users and non-users were required to have at least two PHQ-9 assessments to allow estimation of within-person change. Non-users were selected as comparators because no suitable active comparator existed; users had varied indications, including diabetes and obesity. Although non-users were not restricted to individuals with diabetes or obesity, matching on these factors made them clinically comparable and at similar risk of semaglutide initiation during the same period.

Semaglutide users were matched to non-users using three approaches to address confounding: (1) 1:4 exact matching on diabetes; (2) 1:2 matching on age (±5 years), sex, and diabetes; and (3)

1:1 propensity score (PS) matching using nearest-neighbor matching without replacement with a caliper of 0.1 on the logit of the PS. The PS was calculated by logistic regression using the covariates age, sex, diabetes status, BMI, calendar year of index date, and baseline PHQ-9 score. All post-index PHQ-9 assessments through October 2024 were included, and LMMs were used within each matched set to estimate the average difference in PHQ-9 between semaglutide users and non-users, with negative values indicating greater improvement among semaglutide users.

Secondary analyses descriptively summarized within-person changes in PHQ-9 severity categories from baseline to the last available assessment. Analyses were conducted in Stata versions 17 and 18 (StataCorp, College Station, TX, USA), and Sankey diagrams were generated in R version 4.5.1 (R Program for Statistical Computing) using the *networkD3* package.

5.5 Results

5.5.1 Study Population

A total of 354 PWH who initiated semaglutide and had at least one pre- and one post-initiation PHQ-9 assessment were included (Supplemental Figure 5.1), contributing 1,859 PHQ-9 assessments spanning both pre- and post-initiation periods. The median number of PHQ-9 assessments per person was 5 (interquartile range [IQR]: 3–7), with a median of 1 (IQR: 1–2) post-prescription assessment. PWH completed their PHQ-9 assessment closest to the semaglutide initiation (index) date a median of 5.0 months beforehand (IQR: 1.3–11.9) and their first post-initiation PHQ-9 occurred a median of 3.7 months afterward (IQR: 1.5–7.6). Median pre-initiation look-back period was 36.5 months (IQR: 25.2–43.7), and median follow-up after initiation was 9.4 months (IQR: 4.1–16.1).

Baseline characteristics of the cohort, overall and by depression severity, are shown in Table 5.1. Overall, the mean (SD) age was 54 (10) years, 77% were male, and 62% were of non-White race/ethnicity. At semaglutide initiation, 19% had moderate-to-severe depressive symptoms (PHQ-9 ≥10), and antidepressant use increased with symptom severity, ranging from 38% in the no/minimal group to 70% in the moderate-to-severe group. Most participants had obesity (78%), 60% had diabetes, and 97% had suppressed HIV viral loads (<200 copies/mL). Baseline characteristics were largely similar between the analytic cohort (n=354) and those excluded due to missing ≥1 post-initiation PHQ-9 assessment **(**Supplemental Table 5.1).

Baseline characteristics of PWH who initiated semaglutide, overall and by depression severity are shown in Table 5.1. Overall, the mean (SD) age was 54 (10) years, 77% were male, and 62% were of non-White race/ethnicity. At semaglutide initiation, 19% had moderate-to-severe depressive symptoms (PHQ-9 ≥10), and antidepressant use increased with symptom severity, ranging from 38% in the no/minimal group to 70% in the moderate-to-severe group. Most participants had obesity (78%), 60% had diabetes, and 97% had suppressed HIV viral loads (<200 copies/mL).

5.5.2 Changes in Depressive Symptoms: Overall and by Subgroups

Changes in depressive symptoms following semaglutide initiation, estimated using LMMs, are shown in Table 5.2. In the overall cohort, semaglutide initiation was not associated with significant change in depressive symptoms (average change in PHQ-9 score: −0.1; 95% CI: −0.7, 0.5).

Patterns differed by baseline symptom severity. Among those with no/minimal symptoms at baseline (PHQ-9 score 0-4), there was a small but statistically significant increase in depressive symptoms following initiation (+1.2; 95% CI: 0.5, 1.8). In contrast, symptoms remained generally

stable among PWH with mild (PHQ-9 score 5–9) or moderate (PHQ-9 score 10–14) depressive symptoms and declined in those with moderately-severe to severe symptoms (PHQ-9 score ≥15: −4.7; 95% CI: −7.3, −2.2). Across diabetes, BMI, and antidepressant subgroups, changes were not statistically significant. Exploratory subgroup analyses suggested that PWH with baseline PHQ-9 ≥10 and obesity experienced greater reductions in PHQ-9 scores than those without obesity (Supplemental Table 5.2).

5.5.3 Sensitivity Analysis

Sensitivity analyses evaluating different approaches to handling pre- and post-initiation PHQ-9 measurements were generally consistent with the primary analysis, with a slightly larger reduction observed when pre-treatment measurements were restricted to the 12 months prior to initiation (Table 5.3). Pre-treatment PHQ-9 scores were generally stable (Supplemental Table 5.3).

Stratifying PWH with baseline PHQ-9 scores of 0–4 into 0–1 and 2–4 categories showed that the increase in scores was primarily observed among PWH with baseline scores of 0–1 (n=96; mean change +1.7, 95% CI: 0.8, 2.5), whereas no statistically significant change was observed among those with scores of 2–4 (n=93; mean change +0.6, 95% CI: −0.3, 1.6).

We also examined antidepressant medication use between semaglutide initiation and during follow-up. Overall, antidepressant treatment was relatively stable between semaglutide initiation and the first post-initiation PHQ-9 assessment, with 56 PWH (15.8%) experiencing any prescription change during this interval, including 11 new initiations among baseline non-users. Analyses restricting to PWH with stable antidepressant medication use were consistent with the

primary analysis (Supplemental Table 5.4), indicating that changes in antidepressant therapy during follow-up are unlikely to explain the observed findings.

In additional sensitivity analysis, semaglutide users with baseline PHQ-9 ≥15 were compared with matched non-users. Baseline characteristics of semaglutide users and matched non-users are shown in Supplemental Table 5.5, demonstrating improved covariate balance after matching. Across all matching methods, semaglutide users experienced greater reductions in depressive symptoms compared to matched non-users (Supplemental Table 5.6).

5.5.4 Categorical Shifts in Depression Severity

Among PWH with no/minimal symptoms at baseline, 80% remained stable and 20% worsened to a higher severity category. Of those with mild symptoms, 39% improved, 39% remained stable, and 22% worsened. Half of those with moderate symptoms improved, while 32% remained stable and 18% worsened. Notably, 58% of PWH with moderately-severe to severe symptoms improved to a lower severity category (Figure 5.2, Supplemental Table 5.7).

5.6 Discussion

In this pre-post quasi-experimental study of PWH initiating semaglutide for weight and/or diabetes management, we found no evidence that semaglutide was associated with overall worsening of depressive symptoms. While PWH with no/minimal depressive symptoms experienced a small increase in PHQ-9 scores, the change was minor and unlikely to be clinically meaningful. Symptoms remained largely stable among those with mild or moderate baseline depression and decreased among those with moderately-severe to severe symptoms; however, this subgroup was small and potentially influenced by regression to the mean, limiting confidence

in this finding. These findings, supported by multiple sensitivity analyses, suggest that semaglutide is generally safe with respect to depressive symptoms, even among PWH with baseline depression, which is reassuring given historical concerns that weight loss medications could adversely affect psychiatric health.

Our findings are broadly consistent with previous studies in the general population showing no increased risk of depression with GLP-1RA use. Post hoc analyses of semaglutide 2.4 mg trials in adults with overweight or obesity indicated no increased risk of depressive symptoms or suicidal ideation.[14] However, these trials largely excluded participants with PHQ-9 ≥15, limiting generalizability of the findings to people with severe depression. Similarly, a meta-analysis of 80 randomized controlled trials found no increased risk of depression or suicidality with GLP-1RA and noted small improvements in quality of life.[17]

Observational studies further support the psychiatric safety of GLP-1RA. For example, a cohort study utilizing nationwide register data from Sweden and Denmark found no increased risk of suicide death, self-harm, or incident depression among users of various GLP-1RA vs. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors.[15] Similarly, a large study using the UK Clinical Practice Research Datalink reported no elevated risk of suicidality across multiple GLP-1RA vs. SGLT2 inhibitors or Dipeptidyl Peptidase-4 (DPP-4) inhibitors among people with diabetes.[16] In the U.S., De Giorgi et al. found no increase in incident depression and suicidality with semaglutide compared to other antidiabetic medications.[25] Some evidence also suggests reduced risk of depression and suicidality with GLP-1RA use. A U.S. Medicare study of older adults with diabetes reported a lower risk of depression with GLP-1RA use compared to DPP-4 inhibitors; although findings may not generalize to adults <65 years.[26] Similarly, another study found lower rates of

suicidal ideation with semaglutide compared to other anti-obesity or anti-diabetes medications, though it was limited by confounding by indication and immortal time bias.[27]

Unlike prior studies, which mostly assessed *incident* depression or suicidality, our study examined symptom changes among PWH, including those with pre-existing depression. These findings add evidence of a favorable safety profile for semaglutide in a population often underrepresented in clinical trials, with a high burden of depression and metabolic comorbidities.

The precise mechanisms underlying the observed changes remain incompletely understood. Improvements in depressive symptoms may be partly mediated by weight loss, as also suggested by our subgroup analyses showing more pronounced benefits among PWH with higher baseline BMI. Additionally, preclinical evidence suggests that GLP-1RA, including semaglutide, act directly on the central nervous system by modulating neurotransmitters such as serotonin and dopamine and reducing neuroinflammation, mechanisms that may contribute to improved depressive symptoms.[28–30]

As semaglutide use expands for metabolic indications, clinicians often face uncertainty regarding prescribing in patients with depression. Our results provide preliminary evidence that pre-existing depression may not be considered a contraindication, suggesting semaglutide may be prescribed safely in PWH with minimal risk of worsening depressive symptoms, though treatment decisions should be individualized. For individuals with higher depressive burden, potential mood benefits of semaglutide warrant further investigation. Integrated mental health monitoring alongside metabolic management remains recommended.

Our study has several strengths. It was conducted in a large, multisite cohort of PWH across the US that routinely collects comprehensive data including PROs, such as the PHQ-9. Our within-person design allowed each participant to serve as their own control, effectively adjusting for time-invariant confounders. Assigning the index date at medication initiation limited potential secular trends, as participants start at different calendar times. Unlike many previous studies, we included people with moderate-to-severe depression, enhancing the clinical relevance and generalizability of our findings. In addition, we examined changes in depressive symptoms rather than relying on a diagnosis of incident depression.

Nonetheless, this study has limitations. First, as with any observational study, residual confounding is possible. We could not account for factors such as access to psychological or behavioral therapy or other time-varying influences on depressive symptoms, including changes in substance use or life stressors. Second, the improvements observed among PWH with PHQ-9 ≥15 could partly reflect regression to the mean, a statistical phenomenon in which extreme baseline values tend to move closer to the average on subsequent measurements,[31] rather than true treatment effects. To partially address this, we conducted a matched analysis comparing semaglutide users with non-users, which showed greater improvements among semaglutide users, suggestive of but not definitive of an effect beyond regression to the mean. Importantly, even if some of the observed change is due to regression to the mean, there was no evidence of symptom worsening. Third, the PHQ-9 exhibits a floor effect among individuals with no/minimal depressive symptoms at baseline,[32] which reduces its sensitivity to detect small changes; therefore, the observed small increase among those with no/minimal baseline depression may not reflect a clinically meaningful worsening. Sensitivity analyses further showed that the

increase among PWH with baseline scores of 0-4, was primarily driven by those with scores of 0–1, with no statistically significant change observed among those with scores of 2–4. Fourth, approximately half of the cohort contributed only one post-initiation PHQ-9 assessment, which may limit our ability to evaluate longer-term time trends in depressive symptoms. Fifth, our analysis relied on semaglutide prescription records and did not capture medication adherence or persistence, potentially misclassifying exposure. Several medications we classified as antidepressants are also prescribed for other indications (e.g., insomnia, neuropathic pain, smoking cessation), so some individuals may not have been taking them specifically for depression, which may limit the interpretability of our antidepressant-based subgroups. Sixth, the irregular nature of the data made a more structured design like case-crossover more challenging and so we used pre-post with LMM instead.[33,34] Additionally, we did not assess suicidality or other severe psychiatric adverse events directly, which would require larger sample sizes and longer follow-up. Finally, our findings are generalizable to PWH engaged in care with ongoing mental health monitoring, as inclusion required at least two PHQ-9 assessments.

5.7 Conclusion

Among PWH in routine clinical care, semaglutide initiation was not associated with worsening depressive symptoms, including among those with pre-existing depression. While minor, non–clinically significant changes were observed among those with no or minimal baseline symptoms, depression-related concerns appear minimal, providing reassurance for its use in HIV care. Nevertheless, continued monitoring remains important.

5.8 Tables and Figures

Table 5.1. Demographic and Clinical Characteristics of PWH who Initiated Semaglutide by Depression Status

Characteristic N (%) or Mean (SD)	Depression Status			
	No/Minimal Depression (N=189)	Mild Depression (N=98)	Moderate/Severe Depression (N=67)	Total (N=354)
Age (years)	54.7 (10.4)	52.7 (10.0)	54.3 (9.9)	54.1 (10.2)
Sex				
Female	45 (23.8%)	15 (15.3%)	20 (29.9%)	80 (22.6%)
Male	144 (76.2%)	83 (84.7%)	47 (70.1%)	274 (77.4%)
Race/Ethnicity				
Non-Hispanic White	60 (31.7%)	45 (45.9%)	30 (44.8%)	135 (38.1%)
Non-Hispanic Black	74 (39.2%)	20 (20.4%)	19 (28.4%)	113 (31.9%)
Hispanic	46 (24.3%)	32 (32.7%)	14 (20.9%)	92 (26.0%)
Other	9 (4.8%)	1 (1.0%)	4 (6.0%)	14 (4.0%)
HIV Viral Load				
<200 copies/mL (suppressed)	186 (98.4%)	93 (94.9%)	63 (95.5%)	342 (96.9%)
≥200 copies/mL (unsuppressed)	3 (1.6%)	5 (5.1%)	3 (4.5%)	11 (3.1%)
Baseline CD4 Count	814.8 (363.2)	720.4 (393.1)	885.0 (479.1)	802.0 (398.6)
Nadir/Lowest CD4 Count	277.9 (242.4)	289.1 (235.0)	361.8 (302.4)	296.9 (254.1)
Diabetes Status				
No Diabetes	67 (35.4%)	47 (48.0%)	27 (40.3%)	141 (39.8%)
Diabetes	122 (64.6%)	51 (52.0%)	40 (59.7%)	213 (60.2%)
Treated Dyslipidemia				
No	58 (30.7%)	40 (40.8%)	25 (37.3%)	123 (34.7%)
Yes	131 (69.3%)	58 (59.2%)	42 (62.7%)	231 (65.3%)
Anti-Hypertensive Use				
No	33 (17.5%)	21 (21.4%)	7 (10.4%)	61 (17.2%)
Yes	156 (82.5%)	77 (78.6%)	60 (89.6%)	293 (82.8%)
Body Mass Index				
BMI <30	38 (20.1%)	21 (21.6%)	18 (27.3%)	77 (21.9%)
BMI 30-34.9	67 (35.5%)	40 (41.2%)	21 (31.8%)	128 (36.4%)
BMI ≥35	84 (44.4%)	36 (37.1%)	27 (40.9%)	147 (41.8%)
On Antidepressants				
No	118 (62.4%)	39 (39.8%)	20 (29.9%)	177 (50.0%)
Yes	71 (37.6%)	59 (60.2%)	47 (70.2%)	177 (50.0%)

Abbreviations: PWH (people with HIV)

No/minimal depression: PHQ-9 of 0-4

Mild depression: PHQ-9 of 5-9

Moderate/severe depression: PHQ-9 of ≥10

Table 5.2. Change in Depressive Symptomology After Semaglutide Initiation Among PWH, Overall and Across Subgroups

Subgroup	N	Δ PHQ-9 (95% CI)	p-value
Overall	354	−0.1 (−0.7, 0.5)	0.8
Baseline PHQ-9 severity			
PHQ-9 score 0–4	189	1.2 (0.5, 1.8)	<0.001
PHQ-9 score 5–9	98	−0.3 (−1.5, 0.8)	0.6
PHQ-9 score 10–14	34	−1.0 (−3.3, 1.4)	0.4
PHQ-9 score ≥15	33	−4.7 (−7.3, −2.2)	<0.001
Clinical subgroups			
Diabetes	213	0.03 (−0.7, 0.8)	0.9
No diabetes	141	−0.3 (−1.2, 0.7)	0.6
BMI < 30	77	0.6 (−0.9, 2.1)	0.6
BMI 30–34.9	128	−0.1 (−1.0, 0.8)	0.8
BMI ≥ 35	147	−0.3 (−1.1, 0.6)	0.6
On antidepressants	177	0.02 (−0.9, 0.9)	0.9
Not on antidepressants	177	−0.2 (−1.0, 0.5)	0.6

Note: Estimates are from linear mixed models adjusted for age, sex, race/ethnicity, and time.

PHQ-9: 9-item Patient Health Questionnaire

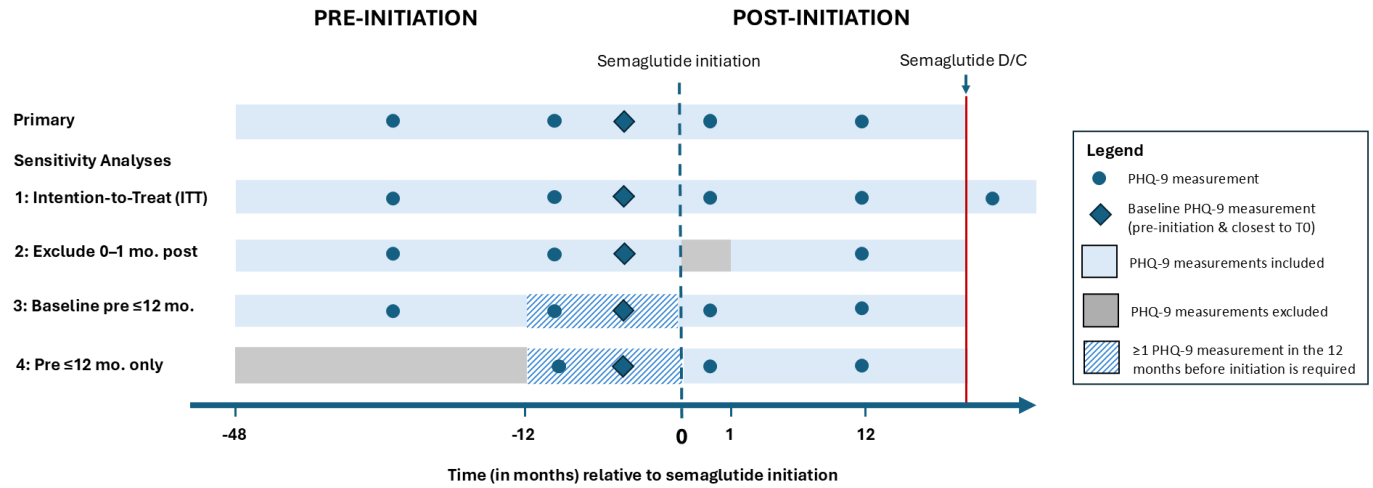
0-4: No/minimal depression

5-9: Mild depression

10-14: Moderate depression

≥15: Moderately severe to severe depression

Figure 5.1. PHQ-9 Assessment Windows for Primary and Sensitivity Analyses.



PHQ-9 assessments that fall within the shaded blue regions are included; assessments that fall within gray regions are excluded. The dashed vertical line (T0) represents semaglutide initiation. The Primary Analysis includes all pre-initiation assessments (up to 4 years before T0) and all on-treatment post-initiation assessments. Sensitivity Analysis 1 includes all post-initiation assessments regardless of discontinuation; Sensitivity Analysis 2 excludes assessments within 0–1 month after T0; Sensitivity Analyses 3 and 4 restrict to participants with ≥1 pre-initiation assessment within 12 months before T0, with Sensitivity 4 further limiting pre-initiation assessments to that window. In all analyses, baseline is the PHQ-9 closest to but before T0, which may occur >12 months before initiation in the Primary Analysis but must fall within −12 to 0 months in Sensitivity Analyses 3 and 4.

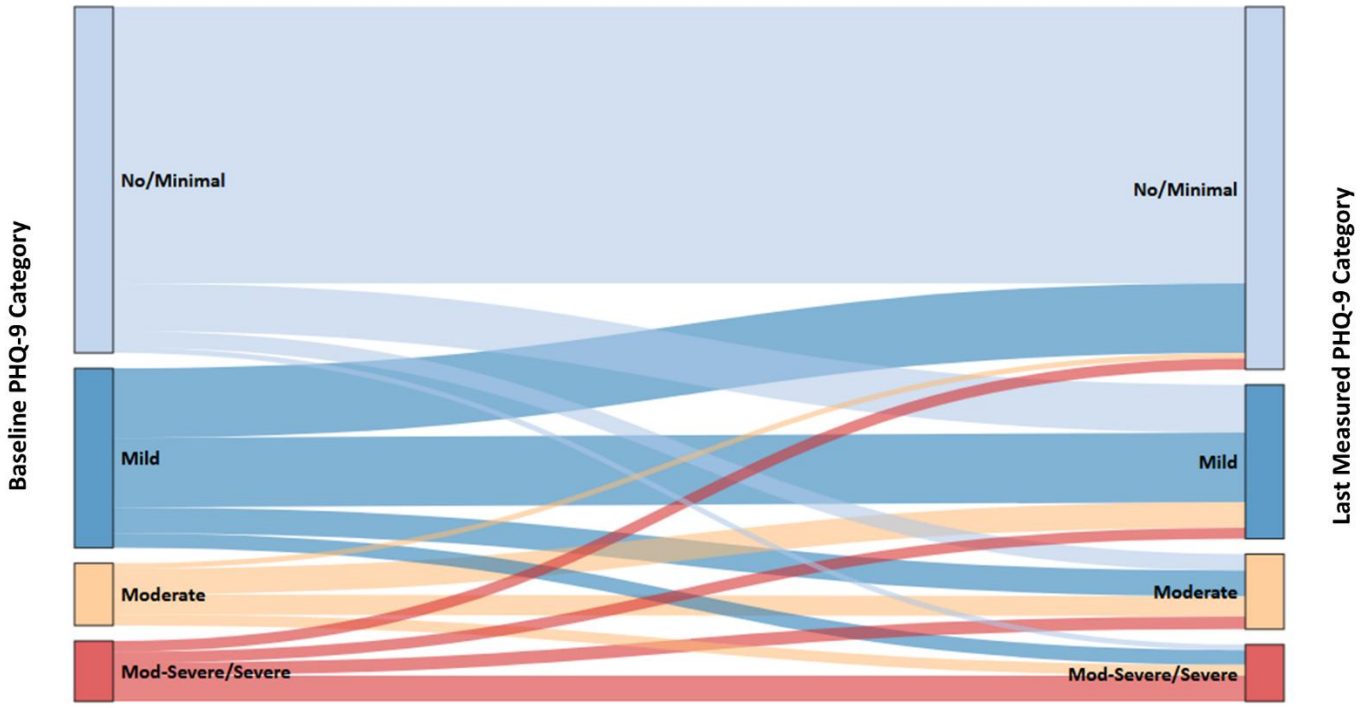
Table 5.3. Sensitivity Analyses of PHQ-9 Change Following Semaglutide Initiation in PWH

Model	N	N observations	Description	Δ PHQ-9 (95% CI)	p-value
Primary Model	354	1,859	Includes all pre-treatment PHQ-9 measurements (up to 4 years prior) and all post-treatment measurements while on semaglutide; baseline defined as assessment prior to and closest to semaglutide initiation.	−0.1 (−0.7, 0.5)	0.76
Sensitivity 1: Intention-to-Treat (All post-initiation included)	354	2,095	Includes all post-treatment PHQ-9 measurements regardless of treatment discontinuation.	−0.004 (−0.6, 0.6)	0.99
Sensitivity 2: Excludes 0–1 Month Post-Initiation	354	1,821	Excludes PHQ-9 measurements within 1 month after semaglutide initiation; all other pre- and post-treatment measurements included.	−0.1 (−0.7, 0.5)	0.72
Sensitivity 3: Closest Pre-Initiation Measurement ≤12 Months	268 [a]	1,539	Only includes participants with ≥1 PHQ-9 measurement within 12 months prior to semaglutide initiation; baseline PHQ-9 (closest pre-initiation measurement) falls within 12 months prior to initiation; all pre- and post-treatment measurements included.	−0.1 (−0.7, 0.5)	0.80
Sensitivity 4: Excludes Pre-Initiation >12 Months	268 [a]	894	Same as Sensitivity 3, but only pre-treatment measurements within 12 months prior to semaglutide initiation are included; all post-treatment measurements included.	−0.7 (−1.5, 0.01)	0.05

Abbreviations: PHQ-9, Patient Health Questionnaire-9; PWH, people with HIV.

[a] Smaller N reflects the requirement of ≥1 PHQ-9 measurement within 12 months prior to semaglutide initiation. Baseline PHQ-9 categories for these participants were: No/Minimal (0–4), n = 143; Mild (5–9), n = 73; Moderate (10–14), n = 29; Moderately Severe to Severe (≥15), n = 23.

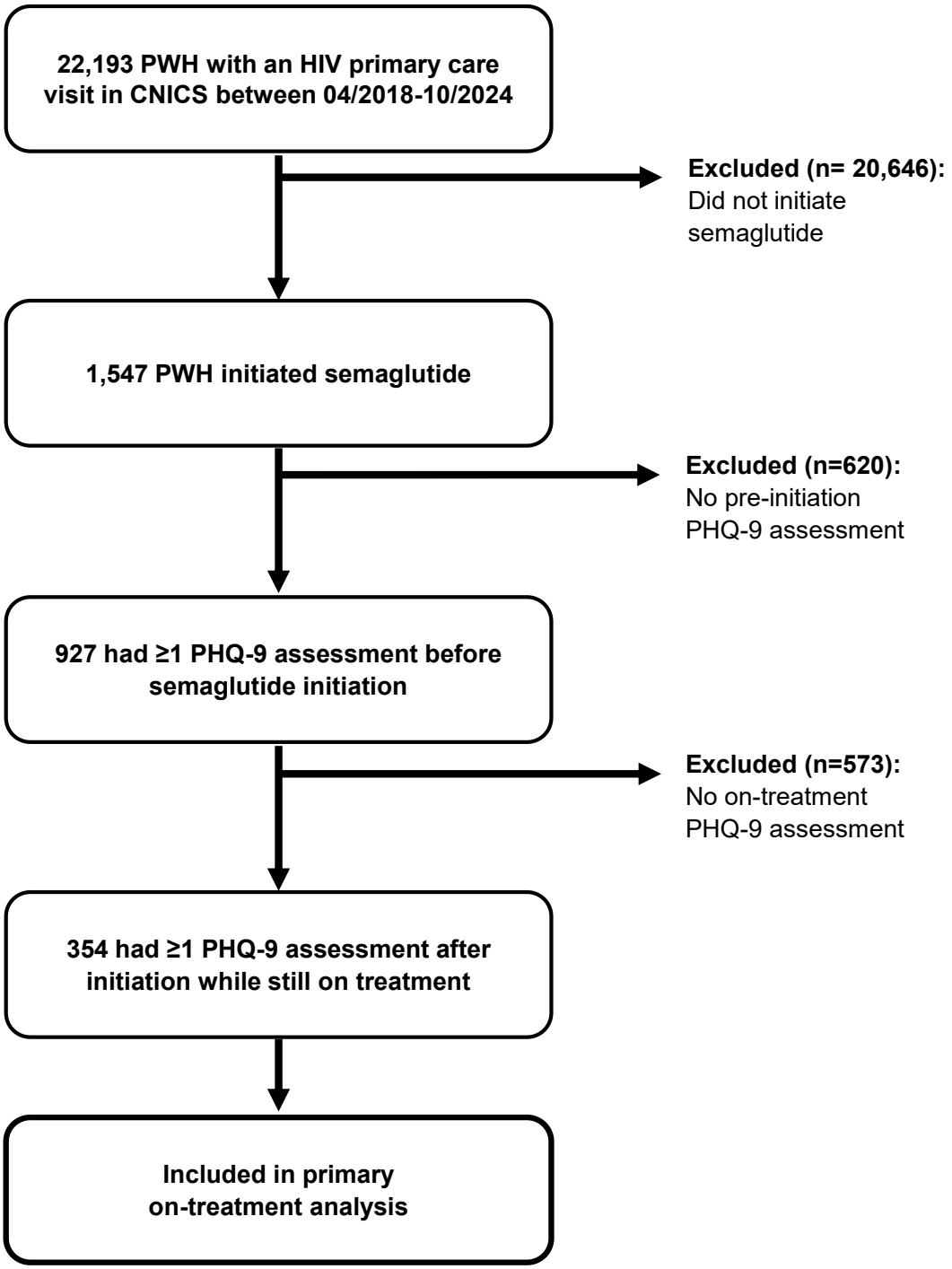
Figure 5.2. Sankey Diagram Showing Transitions Between PHQ-9 Categories from Baseline to Last Follow-up After Initiating Semaglutide



PHQ-9 depression severity categories were defined as: No/Minimal (0–4), Mild (5–9), Moderate (10–14), Moderately Severe to Severe (≥15).

5.9 Supplemental Tables and Figures

Supplemental Figure 5.1. Flow diagram of PWH included in the primary on-treatment analysis following semaglutide initiation



Supplemental Table 5.1. Baseline Characteristics of PWH With and Without Follow-Up PHQ-9 Assessments

Characteristic	Without Follow-up PHQ-9 (n=573)	With Follow-up PHQ-9 (n=354)	Total (n=927)	p-value
Age (mean ± SD)	53.16 ± 10.22	54.06 ± 10.23	53.50 ± 10.23	0.20
Sex				
Male	431 (75.2%)	274 (77.4%)	705 (76.1%)	0.449
Female	142 (24.8%)	80 (22.6%)	222 (23.9%)	
Race/Ethnicity				0.002
Non-Hispanic White	228 (39.8%)	135 (38.1%)	363 (39.2%)	
Non-Hispanic Black	223 (38.9%)	113 (31.9%)	336 (36.3%)	
Latino/a/Hispanic	91 (15.9%)	92 (26.0%)	183 (19.7%)	
Other/Unknown	31 (5.4%)	14 (4.0%)	45 (4.9%)	
Baseline BMI (mean ± SD)	35.84 ± 7.87	34.46 ± 6.18	35.31 ± 7.30	0.005
BMI category				0.321
<30	110 (19.2%)	77 (21.8%)	187 (20.2%)	
30–34.9	192 (33.5%)	128 (36.2%)	320 (34.5%)	
≥35	263 (45.9%)	147 (41.5%)	410 (44.2%)	
Missing	8 (1.4%)	2 (0.6%)	10 (1.1%)	
Diabetes				0.234
No	251 (43.8%)	141 (39.8%)	392 (42.3%)	
Yes	322 (56.2%)	213 (60.2%)	535 (57.7%)	
Baseline PHQ-9 (mean ± SD)	5.57 ± 5.82	5.52 ± 5.35	5.55 ± 5.64	0.91

Supplemental Table 5.2. Exploratory Subgroup Analyses of PHQ-9 Changes After Semaglutide Initiation in PWH: Within Baseline PHQ-9 Severity Strata (0–4, 5–9, ≥10)

Baseline PHQ-9	Subgroup	N	Δ PHQ-9 (95% CI)	p-value
0–4	**BMI <30 kg/m²**	38	2.0 (0.2, 3.7)	0.03
	BMI ≥30 kg/m²	151	1.1 (0.4, 1.8)	0.002
	BMI <35 kg/m²	105	0.9 (-0.0, 1.8)	0.05
	BMI ≥35 kg/m²	84	1.6 (0.6, 2.5)	0.001
	No diabetes	67	1.0 (-0.1, 2.1)	0.07
	Diabetes	122	1.2 (0.4, 2.0)	0.003
	Not on antidepressants	118	1.1 (0.3, 1.8)	0.007
	On antidepressants	71	1.2 (0.1, 2.3)	0.03
5–9	**BMI <30 kg/m²**	21	-0.5 (-3.0, 2.0)	0.7
	BMI ≥30 kg/m²	76	-0.4 (-1.7, 0.8)	0.45
	BMI <35 kg/m²	61	-0.1 (-1.5, 1.3)	0.9
	BMI ≥35 kg/m²	36	-1.0 (-2.9, 0.8)	0.3
	No diabetes	47	-0.9 (-2.4, 0.6)	0.2
	Diabetes	51	0.3 (-1.3, 1.9)	0.7
	Not on antidepressants	39	-1.9 (-3.3, -0.4)	0.01
	On antidepressants	59	0.5 (-0.99. 2.1)	0.5
≥10	**BMI <30 kg/m²**	18	-0.7 (-4.8, 3.5)	0.8
	BMI ≥30 kg/m²	48	-3.3 (-5.2, -1.5)	<0.001
	BMI <35 kg/m²	39	-1.1 (-3.4, 1.3)	0.4
	BMI ≥35 kg/m²	27	-4.5 (-7.0, -1.9)	0.001
	No diabetes	27	-1.7 (-4.6, 1.2)	0.3
	Diabetes	40	-3.3 (-5.4, -1.1)	0.003
	Not on antidepressants	20	-3.8 (-7.4, -0.1)	0.04
	On antidepressants	47	-2.1 (-4.1, -0.1)	0.04

Supplemental Table 5.3. Longitudinal Trends in Depressive Symptoms (PHQ-9) During the Pre-Initiation Period Among People with HIV Who Later Initiated Semaglutide

Group	N	Δ PHQ-9 per Year Before Semaglutide Start	p-value
Overall cohort	354	-0.2 (−0.4 to −0.02)	0.05
PHQ-9 of 0-4	189	-0.5 (−0.8 to −0.3)	<0.001
PHQ-9 of 5-9	98	0.04 (-0.4 to 0.5)	0.86
PHQ-9 of 10-14	34	-0.02 (-0.8 to 0.8)	0.97
PHQ-9 of ≥15	33	0.5 (−0.5 to 1.4)	0.32

Estimates represent the annual change in PHQ-9 scores prior to semaglutide initiation. Negative values indicate a decrease, and positive values indicate an increase in depressive symptoms over time.

Supplemental Table 5.4. Sensitivity Analyses Restricting to PWH With Stable Antidepressant Use

Model	N	N observations	Description	Δ PHQ-9 (95% CI)	p-value
Primary Model	354	1,859	No restriction based on antidepressant use	−0.1 (−0.7, 0.5)	0.76
Stable Antidepressant Use (Baseline to First Post-Initiation PHQ-9)	298	1,575	Restricted to participants with no antidepressant initiation, discontinuation, medication switch, or dose change between semaglutide initiation and first post-initiation PHQ-9	−0.3 (−1.0, 0.4)	0.45
Stable Antidepressant Use (Entire Follow-Up)	234	1,188	Restricted to participants with no antidepressant prescription changes during the entire follow-up period	−0.4 (−1.0, 0.3)	0.27

Supplemental Table 5.5. Baseline Characteristics of Semaglutide Users and Matched Non-Users With Baseline PHQ-9 ≥15, by Matching Method

Variable	Before Matching		After matching					
			1:4 Diabetes Exact Matching		1:2 Age, Sex, Diabetes Matching		1:1 PS Matching	
	Semaglutide (n=33)	Non-user (n=628)	Semaglutide (n=33)	Non-user (n=132)	Semaglutide (n=33)	Non-user (n=66)	Semaglutide (n=28)	Non-user (n=28)
Age, mean (SD)	54.9 (9.5)	48.8 (11.7)	54.9 (9.5)	52.8 (11.5)	54.9 (9.5)	55.2 (8.7)	55.0 (8.3)	54.6 (9.7)
Male, n (%)	24 (72.7%)	537 (85.5%)	24 (72.7%)	103 (78.0%)	24 (72.7%)	48 (72.7%)	19 (67.9%)	20 (71.4%)
Diabetes, n (%)	20 (60.6%)	94 (15.0%)	20 (60.6%)	80 (60.6%)	20 (60.6%)	40 (60.6%)	16 (57.1%)	15 (53.6%)
BMI, mean (SD)	32.8 (7.5)	28.0 (6.1)	32.8 (7.5)	29.7 (7.2)	32.8 (7.5)	30.0 (7.8)	32.5 (7.8)	32.7 (9.4)
PHQ-9, mean (SD)	17.7 (2.0)	18.7 (3.1)	17.7 (2.0)	18.4 (3.0)	17.7 (2.0)	18.3 (2.8)	17.6 (2.1)	17.4 (2.2)
Index Year, n (%)								
2019	0 (0.0%)	98 (15.6%)	0 (0.0%)	18 (13.6%)	0 (0.0%)	6 (9.1%)	0 (0.0%)	0 (0.0%)
2020	1 (3.0%)	225 (35.8%)	1 (3.0%)	50 (37.9%)	1 (3.0%)	24 (36.4%)	1 (3.6%)	1 (3.6%)
2021	8 (24.2%)	166 (26.4%)	8 (24.2%)	32 (24.2%)	8 (24.2%)	21 (31.8%)	8 (28.6%)	7 (25.0%)
2022	11 (33.3%)	63 (10%)	11 (33.3%)	15 (11.4%)	11 (33.3%)	5 (7.6%)	10 (35.7%)	8 (28.6%)
2023	12 (36.4%)	66 (10.5%)	12 (36.4%)	10 (7.6%)	12 (36.4%)	8 (12.1%)	8 (28.6%)	11 (39.3%)
2024	1 (3.0%)	10 (1.6%)	1 (3.0%)	7 (5.3%)	1 (3.0%)	2 (3.0%)	1 (3.6%)	1 (3.6%)
Race/ethnicity, n (%)								
Non-Hispanic White	16 (48.5%)	266 (42.4%)	16 (48.5%)	58 (43.9%)	16 (48.5%)	26 (39.4%)	12 (42.9%)	13 (46.4%)
Non-Hispanic Black	9 (27.3%)	175 (27.9%)	9 (27.3%)	32 (24.2%)	9 (27.3%)	26 (39.4%)	9 (32.1%)	7 (25.0%)
Hispanic	7 (21.2%)	141 (22.5%)	7 (21.2%)	32 (24.2%)	7 (21.2%)	13 (19.7%)	6 (21.4%)	5 (17.9%)
Other	1 (3.0%)	46 (7.3%)	1 (3.0%)	10 (7.6%)	1 (3.0%)	1 (1.5%)	1 (3.6%)	3 (10.7%)

Supplemental Table 5.6. Between-Group Matched Cohort Analysis of Changes in Depressive Symptoms (PHQ-9) Among Semaglutide Users and Matched Non-Users With Baseline PHQ-9 ≥15

Matching Method	Semaglutide Users	Non-Users	Mean Difference in Δ PHQ-9 (95% CI)	P-value
1:4 Matching on Diabetes [a]	33	132	-1.4 (-2.6, -0.3)	0.018
1:2 Matching on Age (±5 years), Sex, Diabetes [b]	33	66	-2.2 (-3.5, -1.0)	0.001
1:1 Propensity Score Matching [c]	28	28	-2.7 (-5.00, -0.5)	0.016

Estimates represent the mean difference in change in PHQ-9 scores between semaglutide users and matched non-users. Negative values indicate greater symptom improvement in semaglutide users.

Model adjustments vary by matching method:

[a] 1:4 diabetes exact matching adjusted for age, sex, BMI, & site.

[b] 1:2 age, sex, diabetes matching adjusted for BMI & site.

[c] 1:1 propensity score matching adjusted for site.

Supplemental Table 5.7. Shift in Depression Severity Categories from Baseline to Last Follow-up

	Last Measured PHQ-9 Category				
Baseline PHQ-9 Category	**No/Minimal n (%)**	**Mild n (%)**	**Moderate n (%)**	**Mod-Severe/Severe n (%)**	**Total n (%)**
No/Minimal, n (%)	**151 (79.9)**	26 (13.8)	9 (4.8)	3 (1.6)	189 (53.4)
Mild, n (%)	38 (38.8)	**38 (38.8)**	14 (14.3)	8 (8.2)	98 (27.7)
Moderate, n (%)	3 (8.8)	14 (41.2)	**11 (32.4)**	6 (17.7)	34 (9.6)
Mod-Severe/Severe, n (%)	6 (18.2)	6 (18.2)	7 (21.2)	**14 (42.4)**	33 (9.3)
Total	198 (55.9)	84 (23.7)	41 (11.6)	31 (8.8)	354

Note: Depression severity categories defined as follows: No/Minimal (PHQ-9: 0–4), Mild (PHQ-9: 5–9), Moderate (PHQ-9: 10–14), and Moderately Severe to Severe (PHQ-9: ≥15).

Bolded cells on the diagonal represent people who remained in the same category.
Cells below the diagonal indicate people who improved (moved to a lower category).
Cells above the diagonal indicate people who worsened (moved to a higher category).

5.10 Contributions of Authors

- **Concept and design:** Lara Haidar, Stephanie A. Ruderman, Joseph AC Delaney, Heidi M. Crane, Sherif Eltonsy
- **Statistical analysis:** Lara Haidar, Stephanie A. Ruderman
- **Manuscript drafting:** Lara Haidar
- **Critical review and revisions:** All authors
- **Supervision:** Sherif Eltonsy, Joseph AC Delaney, Heidi M. Crane

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5.12 Additional Results (Not Included in the Submitted Manuscript)

5.12.1 Depressive Symptom Change by Weight Loss Category and Baseline PHQ-9 Severity

Since semaglutide is known to induce weight loss, we conducted exploratory analyses to examine whether changes in depressive symptoms differed according to the magnitude of weight change during follow-up. Participants were stratified based on whether they experienced ≥5% weight loss by the end of follow-up (using their last recorded weight measurement after semaglutide initiation), and analyses were further stratified by baseline depression severity (PHQ-9 <10 vs. ≥10). Mixed models were used to account for repeated PHQ-9 measurements over time and adjusted for age, sex, and race/ethnicity. Not all participants had available follow-up weight measurements, which reduced the sample size for these analyses. Overall, these exploratory models allowed us to investigate whether improvements in depressive symptoms were related to clinically meaningful weight changes and whether the association differed by baseline depression severity, while acknowledging the limited statistical power due to smaller subgroup sizes.

Among participants with baseline PHQ-9 scores ≥10, those who lost ≥5% of their body weight experienced a statistically significant reduction in depressive symptoms (Δ PHQ-9 = -3.05, 95% CI -5.13 to -0.97, p = 0.004), whereas those with <5% weight loss did not show a meaningful change (Δ PHQ-9 = -1.36, 95% CI -4.65 to 1.93, p = 0.42). In participants with baseline PHQ-9 <10 or in the overall cohort, changes in depressive symptoms were small and not statistically significant regardless of weight loss category. These results suggest that clinically meaningful improvements in depressive symptoms may be most apparent among individuals with elevated baseline depressive symptoms who also experience substantial weight loss.

Additional Table 5.1. Exploratory Analysis: Change in PHQ-9 Scores Following Semaglutide, Stratified by Weight Loss and Baseline Depressive Symptom Severity

Weight Loss	Baseline PHQ-9	N	N observations	Δ PHQ-9 (95% CI)	p-value
<5%	Overall	154	760	0.53 (-0.41, 1.46)	0.27
≥5%	Overall	164	879	-0.20 (-1.04, 0.64)	0.64
<5%	PHQ-9 <10	126	642	1.18 (-0.41, 2.76)	0.16
≥5%	PHQ-9 <10	133	705	0.48 (-0.41, 1.36)	0.29
<5%	PHQ-9 ≥10	28	118	-1.36 (-4.65, 1.93)	0.42
≥5%	PHQ-9 ≥10	31	174	-3.05 (-5.13, -0.97)	0.004

Chapter 6. Thesis Discussion and Conclusion

This thesis aimed to examine the effectiveness and safety of newer antidiabetic medications, specifically Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors, among people with HIV (PWH), a population that faces an elevated burden of chronic diseases including metabolic and mental health disorders.[9,23,97,98,166,191,350–352] Through a series of observational studies using real-world data from a large cohort of PWH from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) in the United States, this thesis investigated the impact of these medications on bodyweight, glycemic control, kidney function, and depressive symptoms in PWH with or without type 2 diabetes and/or overweight or obesity. This chapter summarizes and integrates the key findings across studies, discusses their broader implications, highlights strengths and limitations, and proposes future research directions.

6.1 Summary of Key Findings

The first manuscript (Chapter 2) used a within-person longitudinal design to assess the effects of semaglutide, a novel GLP-1RA, on bodyweight and glycemic control in PWH. Among 222 PWH newly initiating semaglutide, treatment was associated with clinically meaningful weight loss, with an average reduction of -6.47 kg (95% CI −7.67 to −5.18) and a mean percentage bodyweight reduction of -5.72% (95% CI −6.86 to −4.58) at 1 year. Among 157 PWH with a post-index HbA1c value, semaglutide use was associated with a significant reduction in HbA1c of -1.07% (95% CI −1.64 to −0.50) at 1 year. These reductions are comparable in magnitude to those reported in major trials conducted in the general population.

The second manuscript (Chapter 3) uses a new-user active comparator cohort study design to compare GLP-1RAs, SGLT2 inhibitors, and DPP-4 inhibitors with an older class of glucose-lowering therapy (i.e., sulfonylureas).GLP-1RA led to the greatest bodyweight reduction of -4.4% at 1 year, followed by SGLT2 inhibitors, whereas DPP-4 inhibitors and sulfonylureas were associated with minimal weight change. A substantial proportion of individuals on GLP-1RA achieved ≥5% and ≥10% weight loss, reinforcing the use of these agents for obesity management in PWH. These effects closely mirrored those observed in large real-world studies in the general population, suggesting that GLP-1RA are similarly effective in PWH, despite the presence of HIV-related metabolic and inflammatory risk factors.

The third manuscript (Chapter 4) evaluated kidney outcomes following initiation of SGLT2 inhibitors versus other antihyperglycemic medications. In this propensity score–matched cohort study, 295 PWH initiating SGLT2 inhibitors were matched 1:1 to PWH initiating other antihyperglycemic medications, from nine CNICS sites. Acute declines in eGFR were more common among SGLT2 inhibitor initiators than with other antihyperglycemic agents, reflecting the expected “dip” observed in the general population due to hemodynamic changes. Despite this, overall kidney function stabilized over time, suggesting these early changes are transient and not indicative of long-term harm. These findings support the nephroprotective potential of SGLT2 inhibitors in PWH, while highlighting the importance of early monitoring after initiation. Further studies with larger samples and longer follow-up are needed to confirm long-term renal outcomes in this high-risk group.

The fourth manuscript (Chapter 5) used a pre–post quasi-experimental design to assess the impact of semaglutide on depressive symptoms among PWH, given emerging concerns about

potential neuropsychiatric adverse effects of GLP-1RA, particularly semaglutide. Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9), a validated self-reported tool. PHQ-9 scores were obtained from the CNICS Patient-Reported Outcomes (PROs), which are routinely collected approximately every six months as part of standard HIV care. Among PWH initiating semaglutide, mean PHQ-9 scores remained stable overall, indicating no evidence of mood worsening following treatment initiation. PWH without baseline depression experienced a small, non–clinically significant increase in PHQ-9 scores, whereas those with moderate-to-severe baseline depression showed improvements, though the sample size of this group was small. While regression to the mean could possibly explain those improvements in the high depressive symptom group at baseline, sensitivity analyses using a matched non-user comparator group suggested that improvements in PHQ-9 scores were significantly greater among semaglutide users than comparators, supporting the same overall conclusion. Overall, semaglutide appeared safe from a mental health perspective even among PWH with elevated baseline depressive symptoms. These results align with prior evidence in the general population showing no increased risk of depression or suicidality with GLP-1RA, extending this reassurance to a high-risk and underrepresented group. Together, these findings support the safe use of semaglutide in routine HIV care, with ongoing attention to mental health monitoring.

Taken together, the four studies presented in this thesis offer complementary insights into the real-world effects of GLP-1RA and SGLT2 inhibitors among PWH in routine clinical care. Across outcomes including weight, glycemic control, kidney function, and depressive symptoms, the findings converge on a unifying conclusion: newer antidiabetic therapies appear safe and effective in addressing multiple comorbidities in PWH, a population historically underrepresented in

clinical trials and disproportionately affected by chronic diseases. These comorbidities, obesity, diabetes, chronic kidney disease (CKD), and depression, often coexist in PWH and are interrelated through shared risk factors such as chronic inflammation, antiretroviral therapy effects, and metabolic dysregulation. By addressing these interconnected health challenges, GLP-1RA and SGLT2 inhibitors have the potential to improve multiple aspects of health, supporting a more holistic and patient-centered approach to HIV care.

6.2 Clinical, Policy, and Broader Implications

The findings of this thesis have several important implications for clinical care of PWH, a population increasingly affected by obesity, diabetes, CKD, and depression. The consistent and clinically meaningful bodyweight reductions observed with GLP-1RA, particularly semaglutide, supports their integration into the management of obesity and metabolic syndrome in PWH. A substantial proportion of individuals on GLP-1RA achieved ≥5% weight loss which is a clinically relevant threshold associated with improved glycemic control, reduced cardiovascular risk, and better overall metabolic health.[353,354] These effects were comparable to those seen in general population trials, indicating that HIV-related factors such as ART-induced weight gain[86,88] and chronic inflammation[355] do not significantly blunt treatment response. Additionally, semaglutide appeared safe from a mental health standpoint and further research is warranted to investigate the possible antidepressant effects of GLP-1RA.

SGLT2 inhibitors produced modest weight loss in individuals with diabetes, although the effect was less pronounced than with GLP-1RA. Clinically, SGLT2 inhibitors may be selected for their glycemic and broader metabolic benefits, with the understanding that their effects on bodyweight are modest and they are not considered primary agents for weight loss. They also

demonstrated favorable renal safety profile; the expected initial decline in estimated glomerular filtration rate (eGFR), a class effect, was followed by stabilization over time, mirroring patterns seen in HIV-negative populations. While long-term nephroprotection remains to be established in this population, the observed safety trends are reassuring and consistent with broader evidence.

Collectively, these findings support the use of GLP-1RA and SGLT2 inhibitors as multidimensional therapies that address interconnected health priorities in HIV care, weight, diabetes, and kidney function, while not negatively affecting mental health. They also provide a real-world evidence base that enables clinicians to make more confident, evidence-informed prescribing decisions, even in the absence of large, randomized trials in this population. Importantly, by demonstrating differential effects of GLP-1RA and SGLT2 inhibitors across weight, glycemic, renal, and mental health outcomes, the findings support a holistic, patient-centered approach, enabling shared decision-making and individualized therapy tailored to each person's goals and priorities.

Beyond individual prescribing decisions, these findings have important implications for clinical guidelines and health policy. Currently, most recommendations for GLP-1RA and SGLT2 inhibitors are extrapolated from studies in the general population, with limited evidence directly supporting their use in HIV-specific cohorts. Recent HIV guidelines (2024-2-2025)[87,356,357] have begun to incorporate guidance for GLP-1RAs, recognizing their potential for weight and metabolic management in PWH but emphasizing the need for more data on higher doses used for obesity, long-term safety, and effects in those without diabetes.[239,297] The results of this thesis support

these updates by demonstrating meaningful weight loss and, importantly, showing no worsening of depressive symptoms, a finding not previously addressed in current guidelines. These findings could inform future updates to strengthen recommendations for GLP-1RA use in PWH, supporting cautious, individualized prescribing consistent with general population guidance. Such updates could emphasize pairing these therapies with lifestyle strategies such as resistance training and regular physical activity to help preserve lean mass, along with the need for ongoing monitoring of mental health. As further research accumulates, HIV-specific guidelines could more explicitly incorporate recommendations for GLP-1RA use, informed by both efficacy and safety data in this population. For SGLT2 inhibitors, the findings from this thesis provide early reassurance regarding their safety in PWH and may help inform future HIV-specific guidance as longer-term data on kidney outcomes become available. Further research is needed before guidelines can offer stronger, evidence-based recommendations for routine use, but cautious, individualized prescribing consistent with current kidney and diabetes guidance remains appropriate when standard indications exist.

Beyond treating established disease, GLP-1RAs may also have a preventive role, particularly among people with obesity or early metabolic dysfunction. Effective weight management in this population could help prevent downstream complications, including type 2 diabetes, cardiovascular disease, and kidney disease. Recognizing obesity as a chronic disease is essential, yet care is often siloed, and weight management does not always receive the attention it deserves in routine HIV care.[358,359] Moreover, reliance on body mass index (BMI) alone can be misleading in PWH due to altered body composition from antiretroviral therapy and lipodystrophy.[360–366]

Some individuals may have normal BMI but increased visceral adiposity and metabolic risk, while others may have elevated BMI from lean mass rather than fat. Complementary measures, such as waist circumference, and waist-to-hip ratio assessments, may better capture metabolic risk in this population.[360–366]

However, the high cost of GLP-1RA (especially semaglutide and tirzepatide) remains a major barrier to equitable uptake, particularly among individuals from lower socioeconomic backgrounds or groups who face disparities in healthcare access, including those defined by race, ethnicity, or geographic location.[367–372] Evidence on cost-effectiveness is mixed. In Canada, semaglutide has been cost-effective for adults with obesity but no diabetes, though results are sensitive to assumptions about long-term benefits, population characteristics, and pricing.[373] In contrast, analyses of adults with class III obesity (BMI ≥40 kg/m²) or those with preexisting cardiovascular disease (but no diabetes) suggest that current pricing may limit cost-effectiveness, although price reductions could improve economic value.[374,375] Ensuring access to these therapies is essential to translating clinical evidence into real-world benefit, particularly for individuals who face the greatest need and barriers to care, noting that the cost-effectiveness in people with HIV remains unknown.

Finally, the broader implications of this research must be interpreted in the context of who is represented in the data and who benefits the most from novel therapies. The study population primarily included PWH who were in care, virally suppressed, and able to access newer medications, reflecting only a subset of the broader HIV population. Many others remain

undiagnosed, are not consistently engaged in care, or face structural barriers to accessing novel therapies. Key barriers include medication cost, limited specialty access, housing instability, transportation challenges, substance use, and marginalization based on race or 2SLGBTQIA+ identity, all of which are more prevalent among people with HIV. These barriers, rooted in racism, stigma, poverty, and geographic inaccessibility, must be addressed if the benefits of these medications are to be equitably realized.

Structural changes in HIV care delivery are needed to prepare for broader implementation of emerging therapies as evidence grows. This includes integrating metabolic screening and management into routine HIV care, creating a seamless care system with coordinated referrals to specialists, and expanding training and education across clinician disciplines to improve the management of comorbidities in PWH and ensure the safe and appropriate use of GLP-1RAs and SGLT2 inhibitors. Broader public and private drug coverage for evidence-based and cost-effective pharmacotherapies should be considered once their value in people with HIV is confirmed, and health systems should proactively establish frameworks to support early adoption as larger trials confirm safety and efficacy.

Although this thesis draws on data from a large U.S. clinical cohort, the findings have important relevance for the Canadian HIV epidemic. In Canada, cardiometabolic conditions are often managed separately from HIV care, and despite the presence of some team-based or integrated primary care models, services remain largely siloed across infectious disease, primary care, endocrinology, and mental health.[376] Canada's universal, publicly funded health system provides a strong foundation for incorporating GLP-1RAs and SGLT2 inhibitors into HIV care, yet access is constrained by provincial formularies, special authorization processes, and the high out-of-pocket

costs for individuals without diabetes.[377] These challenges are especially pronounced in provinces with high burdens of houselessness and substance use (e.g. Manitoba),[378] where injectable subcutaneous GLP-1RAs pose additional barriers because they require refrigeration, secure storage, and because the injectable format may be unacceptable or triggering for people who inject drugs. Coordinated policy efforts, expanded public drug coverage, and implementation strategies tailored to underserved populations, including those affected by poverty, housing instability, and substance use, will be essential to ensure that the clinical benefits demonstrated in this thesis translate into equitable improvements in long-term health outcomes for PWH in Canada.

Future research should evaluate the long-term effectiveness, safety, and cost-effectiveness of these medications in diverse PWH populations, and assess implementation models that integrate metabolic and HIV care within existing clinical systems. Without such coordinated efforts, advances in comorbidity management risk widening existing health inequities, highlighting the need for HIV care to evolve into a holistic, person-centered model that addresses aging, multimorbidity, and long-term health outcomes alongside infection management.

6.3 Strengths and Limitations

A major strength of this thesis is the use of longitudinal data from a large, diverse cohort of PWH, addressing an important knowledge gap by focusing on a population often underrepresented in clinical trials with a high burden of comorbidities. Several of the studies employed a new-user active-comparator design combined with propensity score matching and regression adjustment. This approach enhances internal validity and helps mitigate confounding by indication and time-related biases, such as immortal time bias and prevalent user selection bias. By aligning

individuals at the point of treatment initiation and maintaining correct temporality between covariate and exposure assessment, this design allows for a clear evaluation of treatment effectiveness and safety in real-world data. However, it is important to note that this design was not used in all four studies. The fourth manuscript employed a pre-post quasi-experimental design, which controlled for fixed individual-level confounders but did not account for time-varying confounding and is subject to limitations of temporal trends and regression to the mean.

Residual confounding and unmeasured variables remain possible limitations across all observational studies. Although propensity score methods and regression adjustment reduce confounding, unmeasured factors such as socioeconomic status, lifestyle behaviors, clinical characteristics, or patient motivation to lose weight could still influence treatment selection and outcomes. Exposure measurement error is another concern; medication dispensation and adherence were not directly measured, and non-adherence would likely bias effect estimates toward the null, making the findings conservative.

A potential limitation relates to the exclusion of individuals without post-baseline measurements, which may introduce selection (collider-stratification) bias.[379] In these studies, the absence of follow-up measurements was likely driven primarily by patterns of HIV care engagement, such as irregular clinic attendance or limited follow-up time, rather than the exposure or outcome itself, suggesting that the missingness is probably a missing completely at random mechanism. However, this assumption may not fully hold, as follow-up could be indirectly associated with patient characteristics such as overall health status, healthcare engagement, or comorbidity burden, which may in turn relate to both treatment selection and outcomes. To partially address this, we compared baseline characteristics of individuals with and without a follow up

measurement; the baseline characteristics were generally similar between individuals with and without follow-up, suggesting limited imbalance in measured confounders and minimal selection bias. While inverse probability of censoring weighting (IPCW)[380] could help address informative censoring, its added value in this setting is likely limited given the similarity between groups. The resulting weights would be expected to be close to one, with minimal impact on bias reduction and a potential loss of precision (i.e., increased standard errors). Nevertheless, residual selection bias due to unmeasured factors cannot be excluded.

Outcome measurement error is also possible. For example, weight assessments could vary due to differences in timing or scale calibration, potentially misclassifying the degree of weight change, as well as variations in measurement practices across sites. Similarly, serum creatinine levels used to estimate eGFR may fluctuate due to biological factors like hydration status or laboratory variability, which could affect renal outcome classification.

Several analyses used change scores as the primary outcome, which has been debated in the methodological literature.[381,382] A key concern is that change scores do not, in general, estimate causal effects in observational data. In this thesis, treatment is initiated after baseline, and baseline measures (e.g., weight) were treated as confounders, as they were associated with both treatment initiation and follow-up outcomes. They are not mediators, as they occur prior to treatment initiation and therefore cannot lie on the causal pathway from treatment to outcome, nor competing exposures, as they are not independent of treatment assignment. Accordingly, all models adjusted for baseline values of the outcome, making the approach equivalent to an ANCOVA framework on the follow-up outcome. Framing the outcome as change was motivated by clinical interpretability, particularly for weight loss outcomes in metabolic research. Moreover,

confounding by indication and channeling bias remain potential sources of bias despite the use of an active comparator design.[339,383,384] Moreover, the follow-up duration was limited for certain outcomes, such as renal outcomes, which requires longer-term follow-up to assess nephroprotection.

Competing events, such as death, were not accounted for in time-to-event analyses. However, given the relatively short follow-up period, such events were expected to be infrequent. In addition, potential delays in the recording of deaths within the U.S. healthcare system may limit the immediate availability of such information during the study period. Overall, the potential for bias from competing events is considered minimal.

One of the included studies (Chapter 4), evaluating the impact of SGLT2 inhibitors on kidney function, used a 1:1 propensity score matching design. It is important to note that this approach estimates the average treatment effect among the treated (ATT), rather than the average treatment effect in the overall population.[385] This affects generalizability, and the results should be interpreted as the effects of SGLT2 inhibitors on kidney function among individuals who initiated them, but do not estimate the counterfactual outcomes had individuals receiving comparator therapies instead initiated SGLT2 inhibitors.

Finally, while the cohort is large and diverse, generalizability may be limited to similar healthcare settings and populations engaged in HIV care with access to newer therapies.

6.4 Future Directions

This thesis highlights the promise of GLP-1RA and SGLT2 inhibitors in improving metabolic and renal outcomes among PWH, but it also raises several important avenues for future research.

First, long-term follow-up studies are needed to assess the durability of weight loss and renal protection. While early outcomes are encouraging, longer observational periods are essential to evaluate sustained effectiveness, safety, and patterns of discontinuation. This includes better understanding of how many individuals stop GLP-1RA and the reasons for discontinuation in real-world HIV care settings. The long-term nephroprotective effects of these therapies in PWH also remain understudied and warrant dedicated investigation. It is also important to determine whether these medications reduce the risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular mortality, in this population, as has been shown in the general population. Future observational studies using rigorous analysis methods, such as propensity score approaches and the target trial emulation framework, are also needed to reduce bias, particularly confounding by indication, measured confounding, and immortal time bias.

Second, safety concerns, including the potential risk of suicidal ideation with GLP-1RA, should be carefully evaluated in this population, especially given the high baseline prevalence of mental health comorbidities among PWH. Ongoing well-designed observational studies can help clarify these risks.

Third, although small clinical trials of semaglutide in PWH have demonstrated promising efficacy for weight loss and diabetes control, larger trials are needed that are adequately powered, diverse, and tailored to the clinical and social contexts of HIV care. These trials should also evaluate cardiovascular and renal outcomes, as well as long-term safety of GLP-1RAs and SGLT2 inhibitors.

Fourth, implementation science studies are needed to translate emerging evidence into real-world practice. Although larger, definitive trials in PWH are still required, the existing preliminary evidence supports early implementation work. These studies can identify barriers and facilitators to integrating GLP-1RAs into routine HIV care incorporating insights from people with lived experience, clinicians, and policymakers. They are particularly important in HIV care settings where high clinical workloads make it difficult to introduce new therapies. Challenges related to clinical workflows, provider knowledge, patient preferences, and cost may also limit uptake. Insights gained can inform future trial design, guide real-world delivery strategies, and help ensure these therapies achieve maximal impact once broader efficacy is established. Importantly, implementation science does not end once strategies are introduced; ongoing evaluation is essential to ensure interventions remain effective, sustainable, and equitable as clinical evidence and care conditions evolve. As more definitive trial data emerge, implementation science can refine and scale successful approaches, ensuring that advances in pharmacotherapy translate into meaningful improvements in health outcomes for PWH.

Fifth**,** pharmacoeconomic evaluations should assess whether the clinical benefits of GLP-1 receptor agonists justify their high cost, especially in publicly funded healthcare systems. These studies can guide policy and reimbursement decisions, ensuring equitable access to novel and effective therapies.

Sixth, future research should actively address the underrepresentation of diverse sex and gender groups. Most participants in our studies were assigned male at birth, highlighting the need to design and conduct studies that are inclusive of women, transgender, and gender-diverse individuals. Applying Sex, Gender, and Diversity-Based Analysis Plus (SGBA+) frameworks can help

capture the nuanced ways in which sex, gender identity, and intersecting social determinants of health shape access to care, treatment responses, and outcomes.

Finally, mechanistic studies are needed to understand how GLP-1RA and SGLT2 inhibitors exert their metabolic and renal effects specifically in PWH, and to identify which subgroups are most likely to benefit. While the core mechanisms of these therapies are established in the general population, HIV-specific factors, such as chronic immune activation, ART-related metabolic effects and alterations in body composition, may modify treatment response, pharmacokinetics, or pharmacodynamics. Elucidating these interactions could inform personalized treatment strategies, optimize therapeutic efficacy, and help predict both responders and non-responders within the HIV population.

In summary, emerging evidence for GLP-1RA and SGLT2 inhibitors in PWH is encouraging. Realizing their full potential will require long-term, inclusive, and interdisciplinary research that addresses not only efficacy but also safety, equity, implementation, and cost-effectiveness.

6.5 Conclusion

This thesis contributes new real-world evidence on the effectiveness and safety of GLP-1RA and SGLT2 inhibitors among PWH, a population that has historically been underrepresented in clinical research despite facing a disproportionate burden of metabolic, renal, and mental health comorbidities. Across four observational studies using data from a large clinical cohort in the US, this thesis examined outcomes ranging from weight loss and glycemic control to kidney function and depressive symptoms. Across these studies, GLP-1RA, particularly semaglutide, were associated with substantial weight loss and improvements in glycemic control, and semaglutide was not associated with overall worsening of depressive symptoms. SGLT2 inhibitors provided

modest weight reduction and were linked to a transient dip in kidney function compared with other antihyperglycemic classes, consistent with an expected early effect that generally stabilizes over time.

Collectively, the thesis findings support a broader shift in chronic disease management in HIV, moving beyond viral suppression to address the complex comorbidities that increasingly define long-term health and quality of life in this population, and emphasize the importance of real-world data for evaluating novel therapies in populations routinely excluded from trials. This work helps fill a critical evidence gap by demonstrating that newer antidiabetic agents have potential benefits in the management of metabolic and renal disease in this population while maintaining a favorable safety profile. Yet, the ability to benefit from these novel therapies remains inequitable, often limited to those already engaged in care and able to access high-cost therapies. Moving forward, the next steps must focus on generating stronger evidence through trials and larger, long-term observational studies that include diverse populations of PWH, particularly women, non-binary and transgender individuals, 2SLGBTQIA+ people, people who use substances including injection drugs, racialized groups, and those outside urban specialty settings. Integrating metabolic care into routine HIV management and expanding equitable access to therapies will be essential, alongside evaluating cost-effectiveness and implementation to guide sustainable use. Centering patient voice and lived experience in future research will ensure that emerging therapies reflect real-world needs and priorities, and embedding more patient-reported outcome measures can help capture the outcomes that matter most to patients. Aligning clinical innovation with equitable access can help transform HIV care into a more person-centered model that supports healthy aging and long-term quality of life for all people living with HIV.

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Thesis Appendix

Appendix A Research ethics (HERB)

RITHIM

Research Improvements Through
Harmonization in Manitoba
A201 Chown Building
753 McDermot Avenue
Winnipeg, MB R3E 0T6

CHIPER HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	AFFILIATED INSTITUTION/DEPARTMENT:	ETHICS #:
Lara Haidar	University of Manitoba/Pharmacy	HS27024 (H2025:219)
APPROVAL DATE: July 10, 2025	**EXPIRY DATE:** July 10, 2026	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. Sherif Eltonsy		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
	Impact of New Antidiabetic Medications Among People with HIV
SPONSORING AGENCIES, FUNDING AGENCIES AND/OR COORDINATING GROUPS: National Institutes of Health (NIH)	

Submission Date of Investigator Documents:	REB Receipt Date of Documents:
May 23, 2025 and July 8, 2025	June 2, 2025 and July 8, 2025

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version (if applicable)	Date
Protocol: Protocol along with proposal as outlined in the REVISED University of Manitoba Bannatyne Campus Research Ethics Board Submission Form for Retrospective Chart or Records Review (dated July 8, 2025) and Letter of Response dated July 8, 2025	V. 2	230525
Consent and Assent Form(s):		
Other: Data extraction sheet	V. 1	043025

CERTIFICATION
The above-named research study/project has been reviewed in a ***delegated manner*** by CHIPER HREB and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, CHIPER HREB.

HREB ATTESTATION
CHIPER is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, CHIPER complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Compliance Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

1

CONFLICT OF INTEREST
No Principal or Co-Investigators of this study who are members of CHIPER HREB participated in the review or approval of this study.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. An Annual Study Status Report** must be submitted to CHIPER within 15-30 days of this expiry date.
5. Any changes to the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to CHIPER for consideration in advance of implementation of such changes on the **Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to CHIPER in accordance with its Standard Operating Procedures.
7. The CHIPER must be notified regarding discontinuation or study/project closure on the **Final Study Status Report.**

Sincerely,

[redacted]