

GLP-1 Receptor Agonists: Implications for Metabolic Syndrome in People with HIV



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Brown reported serving as a consultant to ViiV Healthcare, Merck & Co, Inc, Janssen Pharmaceuticals, EMD Serono, and Johnson & Johnson. (Updated September 21, 2026)

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Learning Objectives

After attending this presentation, learners will be able to:

- Define metabolic syndrome and explain how this definition has evolved over time
- Describe the use and potential adverse effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in management of the components of metabolic syndrome

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What is the Metabolic Syndrome?

Low levels of HDL cholesterol.

Elevated blood sugar levels.

High blood pressure.

Excess weight in abdomen.

Hypertriglyceridemia.

Cleveland Clinic

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What are the origins of the metabolic syndrome?

- Early 1900s: Excess adiposity associated with increased mortality.

Relative Risk of Mortality

Percent Deviation

Men

Women

Association of Life Insurance Medical Directors, 1913

Bray, Obesity, 1995

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What are the origins of the metabolic syndrome?

- 1947: Fat distribution is an important determinant of health

SEXUAL DIFFERENTIATION.
A DETERMINANT FACTOR OF
THE FORMS OF OBESITY

By Jean Vague, Marseilles

Vague, Presse Medicale, 1947

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What are the origins of the metabolic syndrome?

- 1988: Clustering of hypertension, dyslipidemia (high TG, low HDL-c) related to insulin resistance and is a major CVD risk factor.

Reaven, Diabetes, 1988

Banting Lecture 1988

Role of Insulin Resistance in Human Disease

GERALD M. REAVEN

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What are the origins of the metabolic syndrome?

- 1989: Linking central adiposity with metabolic risk factors

Kaplan, Arch int Med, 1989

The Deadly Quartet

Upper-Body Obesity, Glucose Intolerance, Hypertriglyceridemia, and Hypertension

Norman M. Kaplan, MD

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Question 1: Abdominal obesity is a required criterion of the metabolic syndrome?

A) Yes
B) No
C) It depends

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Risk Factors	NCEP-ATP III criteria* (2001)	IDF consensus criteria* (2005)
Abdominal obesity	Waist circumference ≥90cm in males and ≥80cm in females (Asian specific cut-offs)	Waist circumference ≥90cm in males and ≥80cm in females (Asian specific cut-offs)
Blood Pressure	≥130/85mm Hg	≥130/85mm Hg
Glucose intolerance	Fasting glucose ≥ 100mg/dL or pre-existing diabetes	Fasting glucose ≥ 100mg/dL or pre-existing diabetes
Triglycerides	≥150mg/dL	≥150mg/dL
HDL-cholesterol	<40 mg/dL males <50 mg/dL females	<40 mg/dL males <50 mg/dL females
Definition of metabolic syndrome	At least 3 risk factors	Abdominal obesity plus 2 or more risk factors

*NCEP-ATP III (2001) - National Cholesterol Education Program - Adult treatment Panel III criteria for metabolic syndrome
*IDF consensus criteria (2005) - International Diabetes Federation criteria for metabolic syndrome

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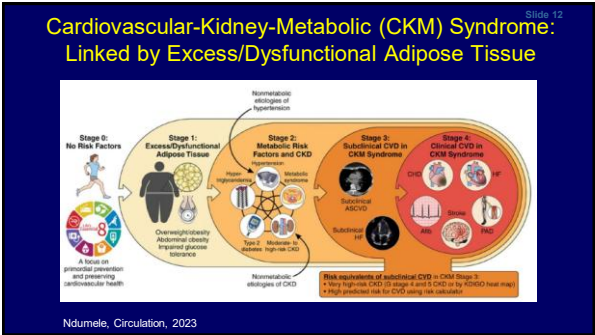
Circulation

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CKM-Related Events More Common in PWH

Journal of the American Heart Association

Research Article | November 14, 2019

ORIGINAL RESEARCH

HIV Infection and Incidence of Cardiovascular Diseases: An Analysis of a Large Healthcare Database

Robert A. Rasmussen, MD, PhD, A. Elise Barnes, MPH, Justin L. Gural, PhD, MPH, Aron Shah, MD, MSc, Eric Yau-Fai Shao, MPH, Vincent Moriconi, MD

Table 3. Association of HIV infection status with incidence of cardiovascular disease, MarketScan 2009 to 2015

	CVD Hospitalization	Myocardial Infarction	Heart Failure	Stroke	Peripheral Artery Disease	Atrial Fibrillation
Model 1	2.0 (1.7–2.2)	1.3 (0.9–1.9)	3.5 (2.7–4.6)	3.0 (2.0–4.5)	1.4 (0.9–2.1)	1.3 (1.1–1.6)
Model 2	1.7 (1.5–2.0)	1.3 (0.9–1.9)	3.2 (2.4–4.2)	2.7 (1.7–4.0)	1.1 (0.7–1.7)	1.2 (1.0–1.5)
Model 3	1.6 (1.3–1.9)	1.2 (0.8–1.8)	2.8 (2.0–3.8)	2.3 (1.5–3.6)	0.9 (0.5–1.4)	1.3 (1.0–1.7)

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Many CKM Conditions Common in PWH

Stage 1

- Adipose Dysfunction
- Pre-Diabetes
- Central Adiposity
- Ectopic Fat Deposition
- Proteinuria

Stage 2

- Metabolic Syndrome
- Hypertriglyceridemia
- Type 2 Diabetes Mellitus
- Chronic Kidney Disease

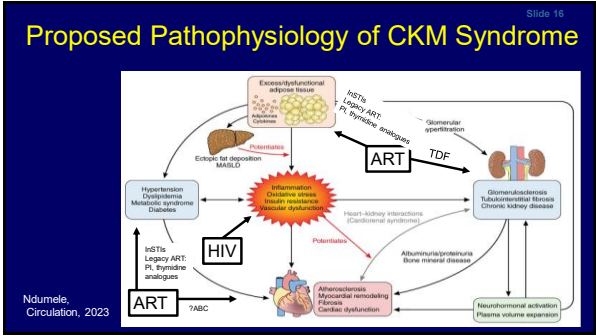
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Proposed Pathophysiology of CKM Syndrome

Ndumele, Circulation, 2023

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AHA Presidential Advisory: Cardiovascular-Kidney-Metabolic Health

Table 2. Risk-Enhancing Factors for CKM Syndrome*

Chronic inflammatory conditions (eg, psoriasis, RA, lupus, HIV/AIDS)
High-risk demographic groups (eg, South Asian ancestry, lower socioeconomic status)
High burden of adverse SDOH
Mental health disorders (eg, depression and anxiety)
Sleep disorders (eg, obstructive sleep apnea)
Sex-specific risk enhancers (beyond gestational diabetes consideration in stage 1)
History of premature menopause (age <40 y)
History of adverse pregnancy outcomes (eg, hypertensive disorders of pregnancy, preterm birth, small for gestational age)
Polycystic ovarian syndrome
Erectile dysfunction
Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L, if measured)
Family history of kidney failure; family history of diabetes

CKM indicates cardiovascular-kidney-metabolic; RA, rheumatoid arthritis; and SDOH, social determinants of health.

*These factors increase the likelihood of progression along CKM stages with associated risk for cardiovascular disease and kidney failure.

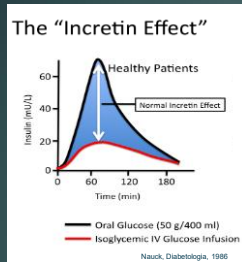
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Can GLP-1 RAs impact the CKM syndrome?

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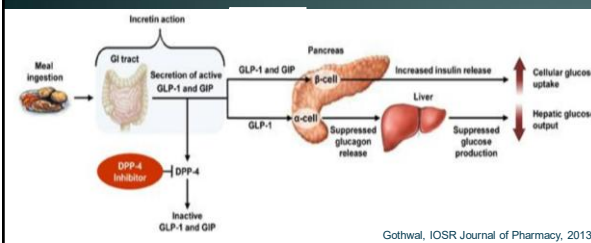
What are Incretins?



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Incretins: Mechanisms of Action



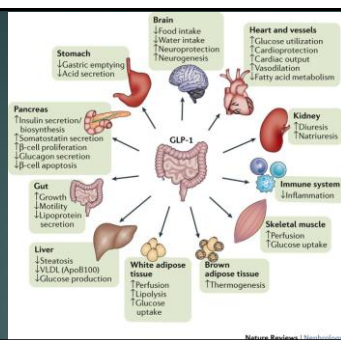
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Multiple Sites of Action of GLP-1 RA

Muskiet, NatureReviewsNephrology, 2017

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GLP1 RAs in Diabetes: Effects on Glucose and Weight			
Drug	Duration	Glucose Effect	Weight Effect
Exenatide	24 weeks	-0.9%	-2.9 kg
Liraglutide	52 weeks	-1.1 %	-2.5 kg
Lixisenatide	24 weeks	-0.72%	-2.7 kg
Dulaglutide	36 weeks	-1.8%	-4.6 kg
Semaglutide	40 weeks	-2.1%	-6.4 kg
Tirzepatide	40 weeks	-2.3%	-11.2 kg

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Glucose and weight data from FDA Package Inserts at highest approved dose

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GLP1 RAs in Diabetes: Effects on CV Outcomes				
Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12% (1.5 mg)
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26% (1 mg)
Tirzepatide	40 weeks	-2.3%	-11.2 kg	Equivalent to Dulaglutide

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Glucose and weight data from FDA Package Inserts at highest approved dose

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GLP1 RA for Obesity			
Drug	Duration	Max Dose	Weight Effect
Liraglutide	72 w	3.0 mg	-8.4 kg/-8%
Semaglutide	68 w	2.4 mg	-18.4 kg/-16%
Tirzepatide	72 w	15 mg	-22 kg/-18.4%
Oral Semaglutide	68 w	50 mg	-15.8 kg/-15.1%
Orforglipron	72 w	36 mg	-11.6 kg/-11.2%

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Pi-Sunyer, NEJM. 2015; Wadden, JAMA, 2021; Wadden, Nature Med, 2023; Knop, Lancet, 2023; Warton, NEJM. 2025

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Semaglutide decreases MetSyn Components in PWH: SLIM Liver Study

Outcome	Baseline	Week 24	Absolute Difference (95% CI)
Waist Circumference (cm)	115	108	-6.7 (-8.5, -4.8)
Fasting Glucose (mg/dL)	100	90.5	-9.9 (-14.7, -5.1)
Triglycerides (mg/dL)	150	131	-26.8 (-46, -7.5)
HDL-c (mg/dL)	46	47.6	2.0 (-0.02, 4.1)
HOMA-IR	5.4	3.9	-1.5 (-3.2, 0.3)

Lake, Annals of Int Med, 2025

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Semaglutide decreases MetSyn Components in PWH with Central Fat Accumulation

PERCENTAGE CHANGE VS PLACEBO

Component	Percentage Change vs Placebo
Waist Circ	-8.30%
Fasting Glucose	-3.60%
TG	-20.70%
HDL-c	-8.10%
BPP	-5.20%

Eckhart, Lancet Diabetes Endocrinology, 2024

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GLP1RA for Obesity-related Conditions

Condition	Efficacy	FDA approval	Comments
CVD	↓ 20% MACE (SELECT)	Semaglutide	Secondary Prevention
Heart Failure	↑ 13% Clin Summary Score ↓ 40% HF Events		Preserved Ejection Fraction
MASH	↓ 29% Steatohepatitis Resolution ↓ 14% Fibrosis	Semaglutide	
Chronic Kidney Disease	↓ 20% albuminuria ↓ 22% in composite kidney endpoint (FLOW)		FDA approved for diabetic kidney disease (semaglutide)

MACE: Major Adverse Cardiovascular Event; MASH: Metabolic-Dysfunction Associated Steatohepatitis

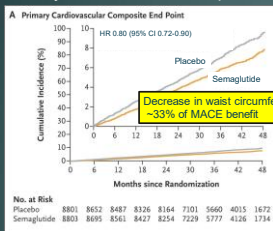
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Kosiborod, NEJM, 2023; Kosiborod, Lancet, 2024; Sanjay, NEJM, 2025; Mathews, NEJM, 2024; Apperloo, Nature Med, 2025

CROI 2026

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Are CVD benefits of GLP-1 RAs mediated by weight loss? : SELECT Trial

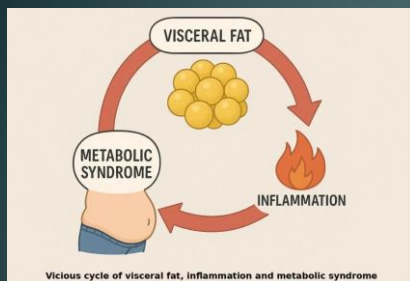
Primary Cardiovascular Endpoint



MACE: CVD death, non-fatal MI, non-fatal stroke
Deanfield, Lancet 2025
Lancett, NEJM, 2023

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Question 2: Which of the following best characterizes the effect of GLP-1 RAs on systemic inflammation?

- A) GLP-1 RAs do not decrease markers of systemic inflammation
- B) GLP-1 RAs decrease markers of systemic inflammation but this is entirely related to the decrease in fat mass.
- C) GLP-1 RAs decrease markers of systemic inflammation but this is only partially related to the decrease in fat mass.

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GLP-1 RA decrease markers of systemic inflammation in people with and without HIV

Slide 31 Wong, JCI, 2025

Funderburg, OFID, 2025



GLP-1 RA Induces Gut T-Cell and Epithelial Remodeling in PWH From a Clinical Trial in South Africa

Healthy

Gut microbiota

CD4⁺ T-cells

Stem cells

Lamina propria

Homeostatic gut microbiota
Tissue resident CD4⁺ and CD8⁺ T-cells
Immunoreactive B-cells
Stem cell-mediated gut renewal

HIV-1 infection

HIV-1

Inflammation
Tissue damage

Microbial translocation

Loss of tissue CD4⁺ T-cells
T-cell activation and dysfunction
Loss of gut stem cell renewal

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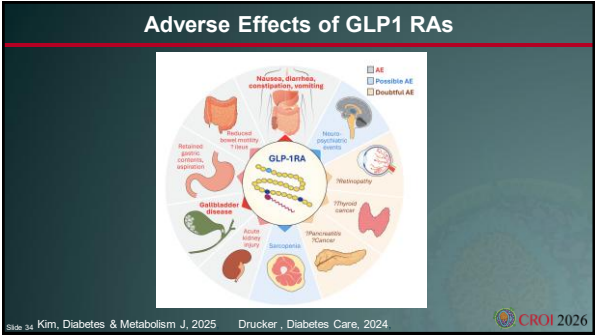
Marin, CROI 2026, #115

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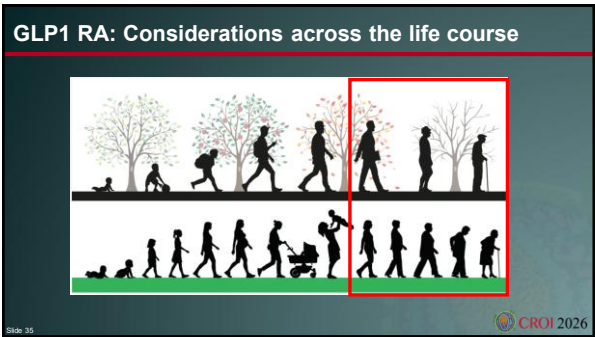
Marin, CROI 2026, #115

GLP-1 RA Induces Gut T-Cell and Epithelial Remodeling in PWH From a Clinical Trial in South Africa

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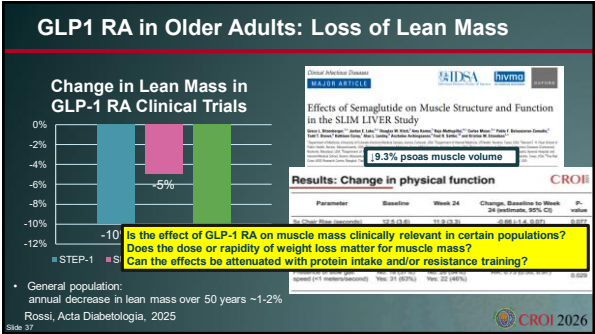
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FDA Package Insert; Section 8.5: Geriatric Use

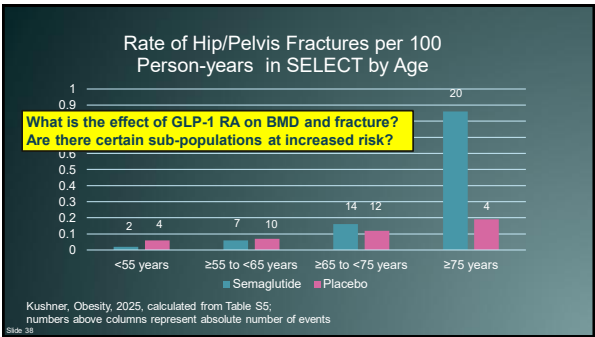
Population	Drug	Trial	> 65 years	>75 years
Diabetes	Dulaglutide	Glycemic Control	19%	2%
		CVOT	53%	10%
	Semaglutide	Glycemic Control	24%	3%
		CVOT	48%	10%
Obesity	Tirzepatide	Glycemic Control	19%	2%
		Weight Reduction	9%	1%
	Semaglutide	CVOT (SELECT)	30%	8%
		MASH	26%	2%
	Tirzepatide	Weight Reduction	9%	0.5%
		OSA	Not reported	

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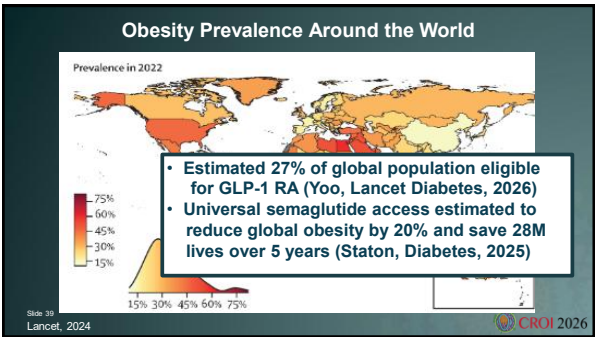
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Access: Achilles' Heel of GLP-1 RAs

Rapidly changing landscape may decrease cost, increase production and improve access

- New oral formulations: Oral semaglutide, Orforglipron (small molecule)
- Patent Expirations: Semaglutide: 2026 in India, China, Brazil, Canada, Turkey; 2032 in US
- Development of multi-agonists
 - GLP-1 RA/(GIP RA) + Amylin, Glucagon, IGF-1, GDF-15, FGF-21, Activin, NPY
- > 60 GLP-1 based compounds in development for multiple indications

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Conclusions

- PWH have a high prevalence of metabolic syndrome and CKM-related events
- GLP-1 RAs improve metabolic syndrome components in PWH and may impact CKM-events (CVD, renal disease, MASLD, heart failure)
- GLP-1 RA improve systemic inflammation in PWH
- Muscle and bone effects in older PWH need more attention
- Access is a critical issue

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Q and A Session



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