

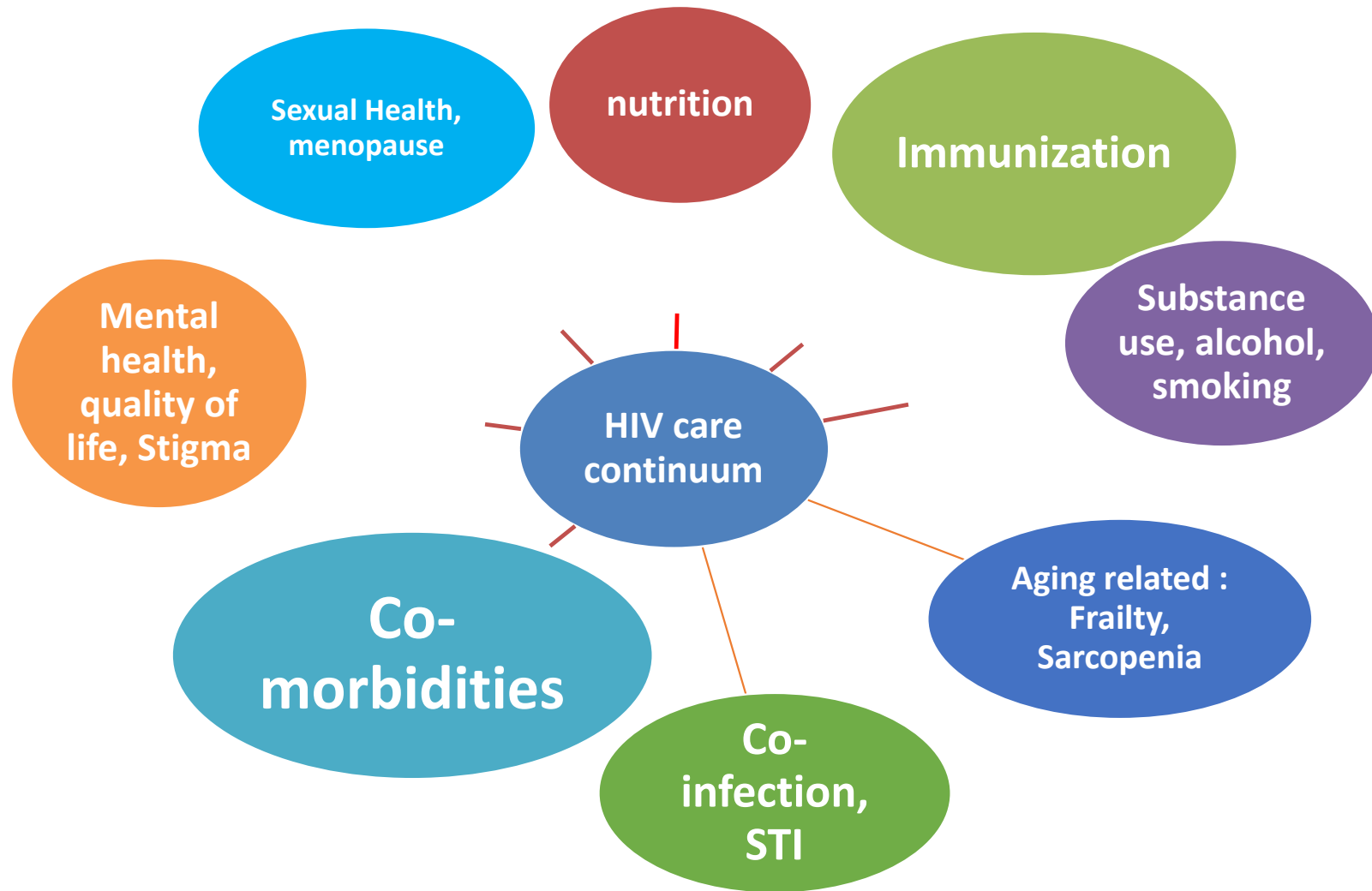
Clinical Care Beyond Viral Suppression

Anchalee Avihingsanon, MD, PhD

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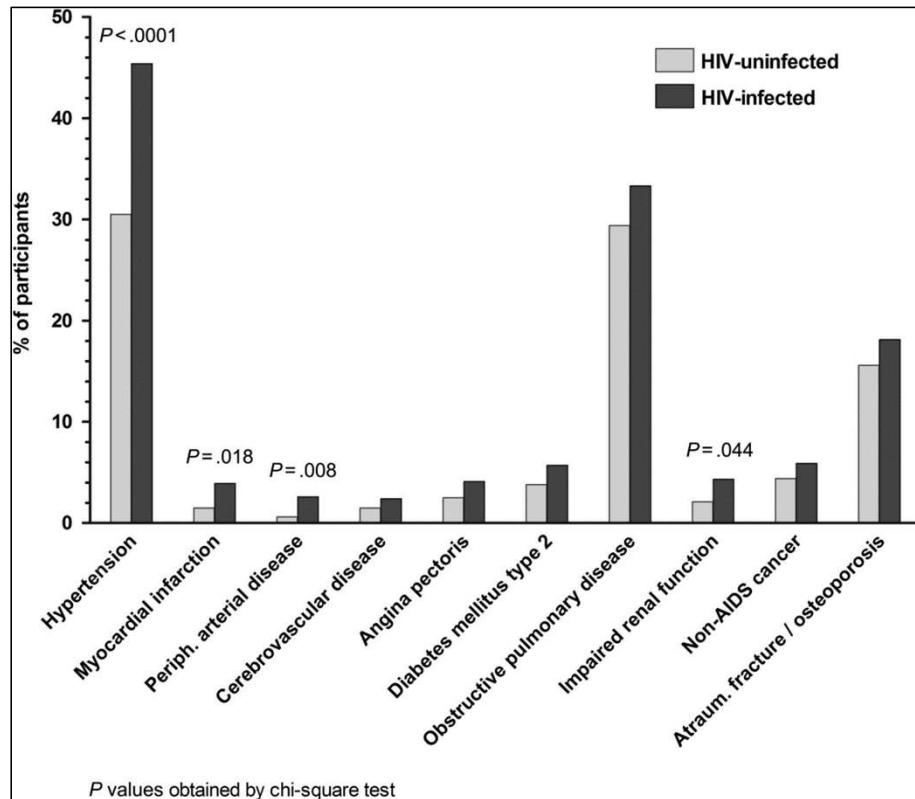
25 Aug 2023

Clinical Care Beyond Viral Suppression : Healthy HIV



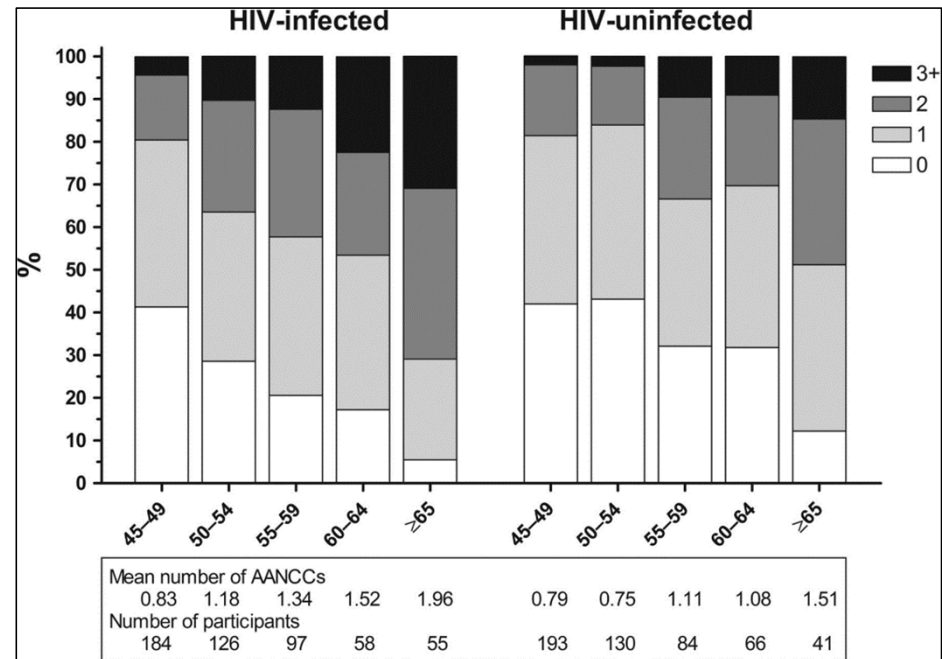
Cross-sectional Comparison of Comorbidity Prevalence The AGE_hIV Cohort Study

Comorbidity Prevalence by HIV Status



Comorbidities with Increased Prevalence

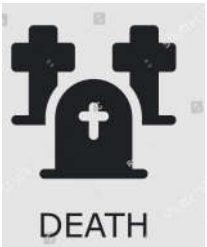
- HTN
- CVD
- Peripheral Artery Disease
- CKD



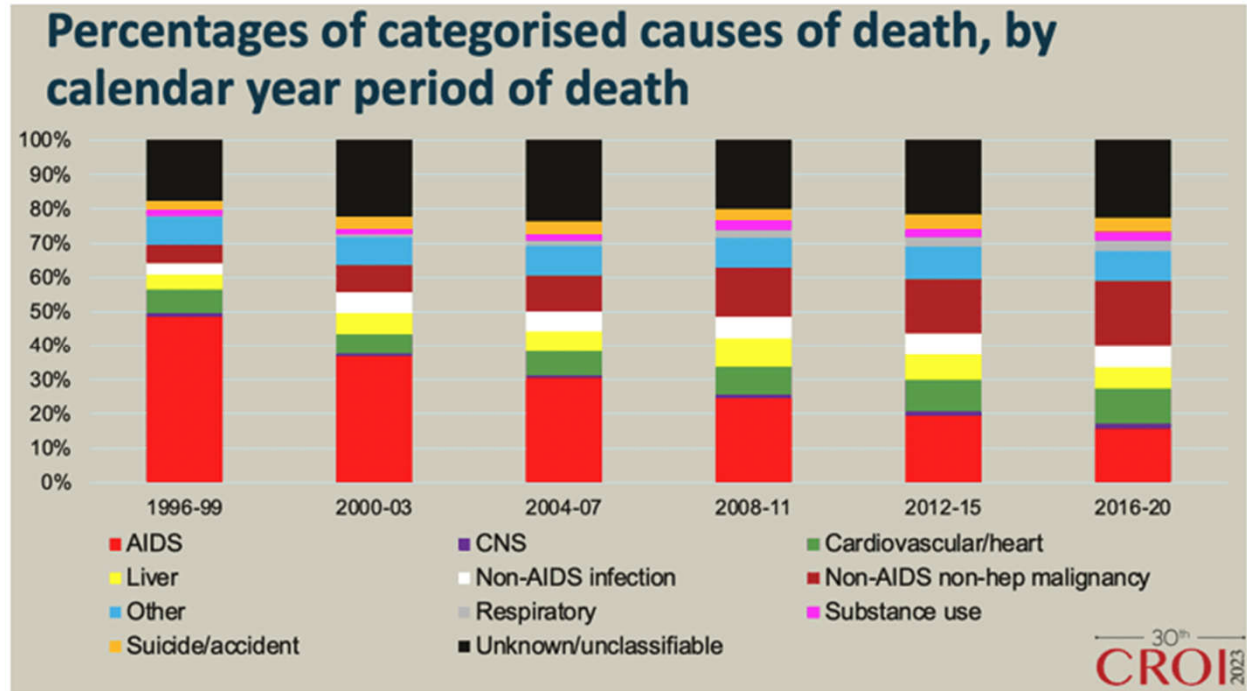
HIV appears to accelerate the prevalence of Multimorbidity

Trends in Mortality in PWH – 2016 to 2019

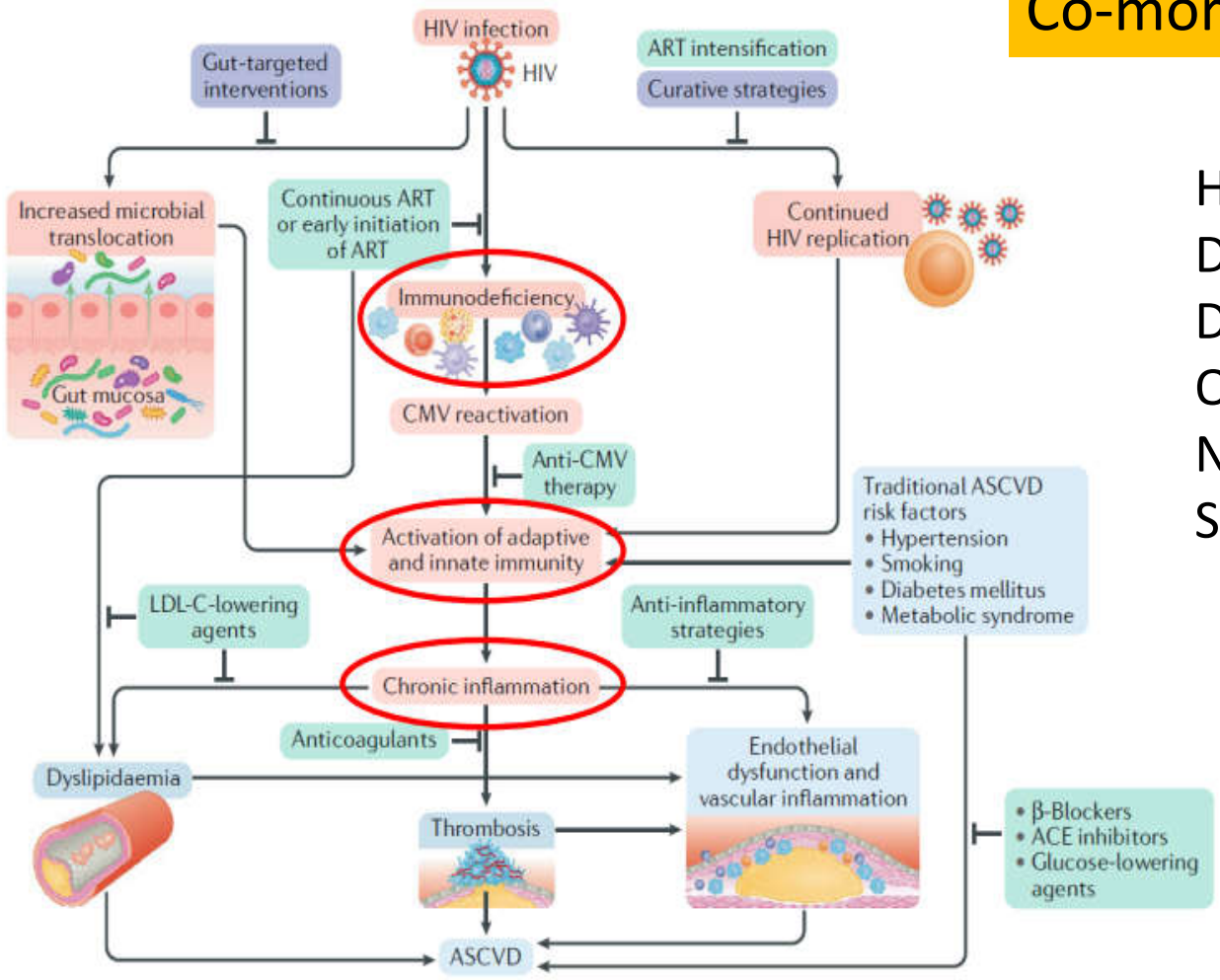
N=189,916 PWH, 16,897 died



- Age at death : 42.2 years in 1996-99 → 56.2 years in 2016-19
- Mortality rate per 1000 PY: 16.9 → 7.9.

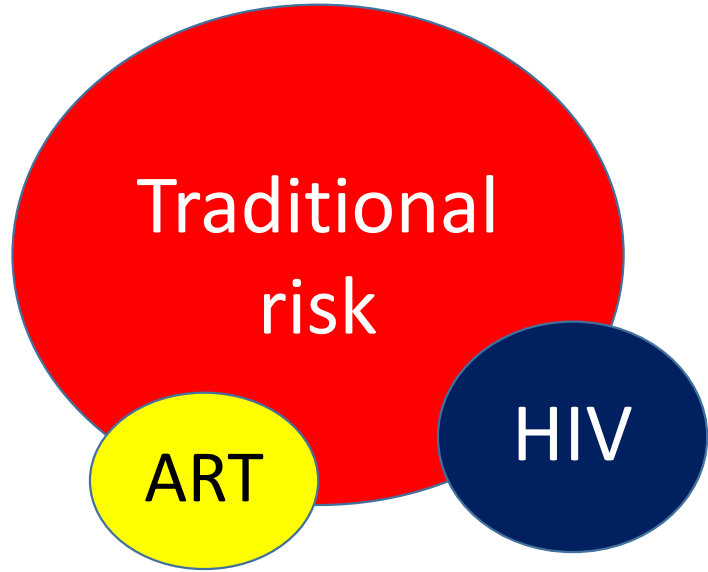


Co-morbidities : Cardiovascular disease



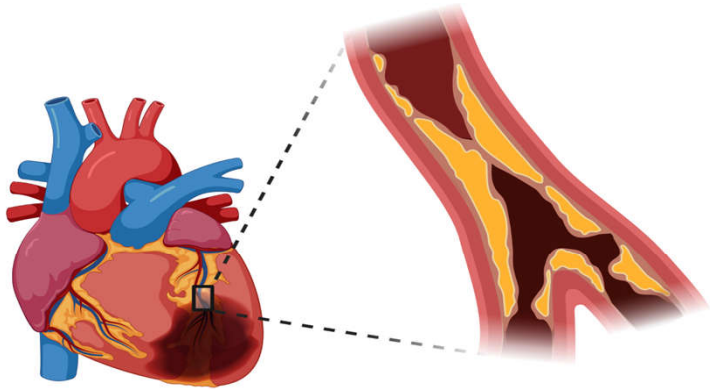
- Hypertension
- Diabetes Mellitus
- Dyslipidemia
- Obesity, weigh gain,
- NAFLD
- Smoking

NASH :
CVD enhancer

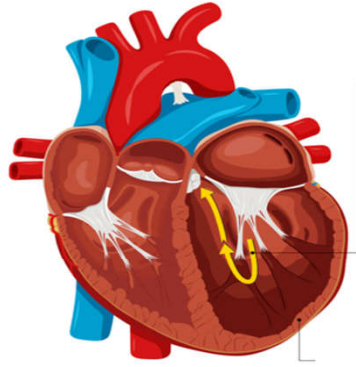


CVD is unique in the setting of HIV disease

Common, Highly Morbid CVD Outcomes ↑ in HIV



Coronary Artery Disease and Myocardial Infarction (MI)



Heart Failure



Arrhythmia and Sudden Cardiac Death

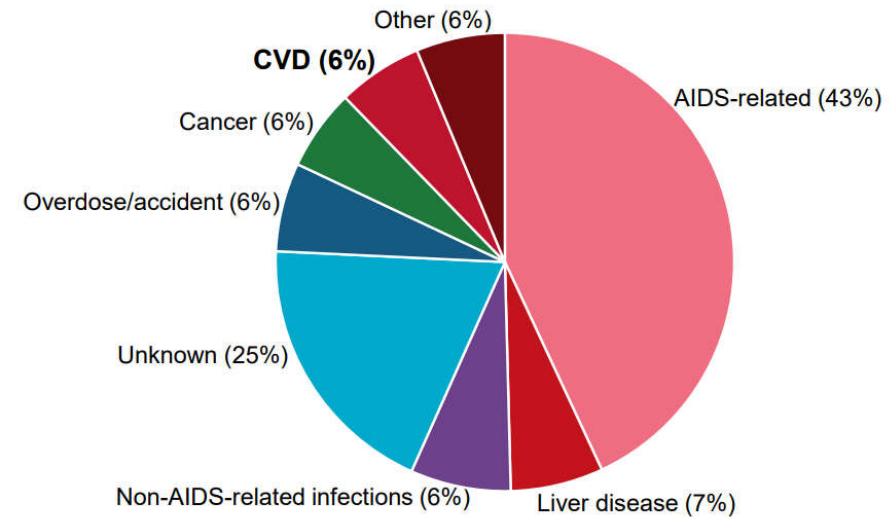
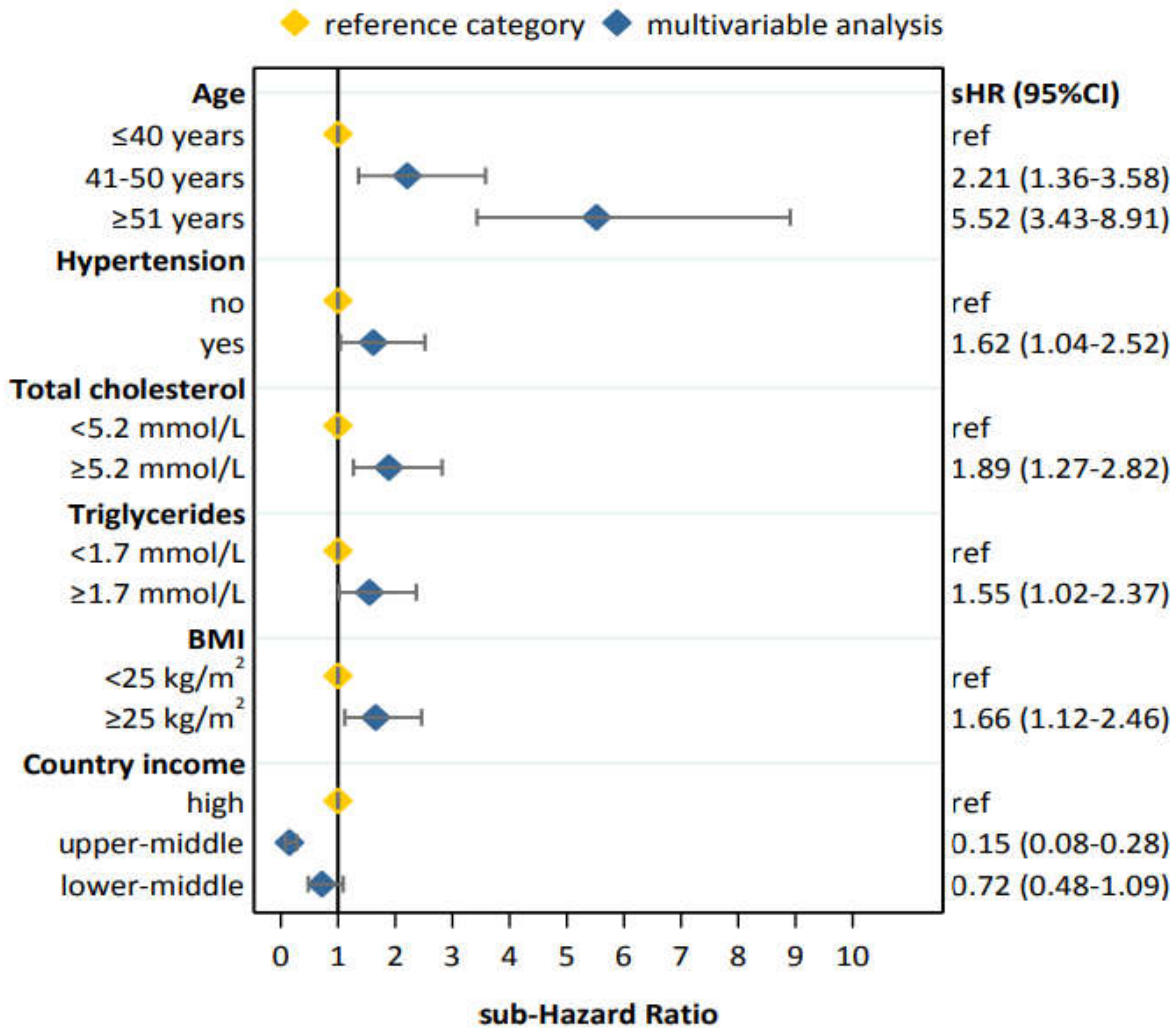
-High sensitivity troponin and subclinical CAD in older PLWH in Thailand¹

- 50% had CAC>0
- 10% had CAC>100

CAC: coronary artery calcium

- REPREIVE²: N 7720, 15% Asian, 44% had ECG abnormal
 - **QTc prolongation** was more common in **male (9% vs 6%)**
 - Nearly twice (**12%) in Asian** compared to non Asian (7%)
 - VL > 400 had twice the odds of prolong QTc (OR2.05)
- ³ HIV-NAT cohort Thailand : prevalence of QTc prolongation was 22.7% : Older age, female, higher BMI

Factors associated with CVD in the TREAT Asia HIV Observational Database (TAHOD) 2003-2017 (N=8069, 378 deaths)



Not significant:

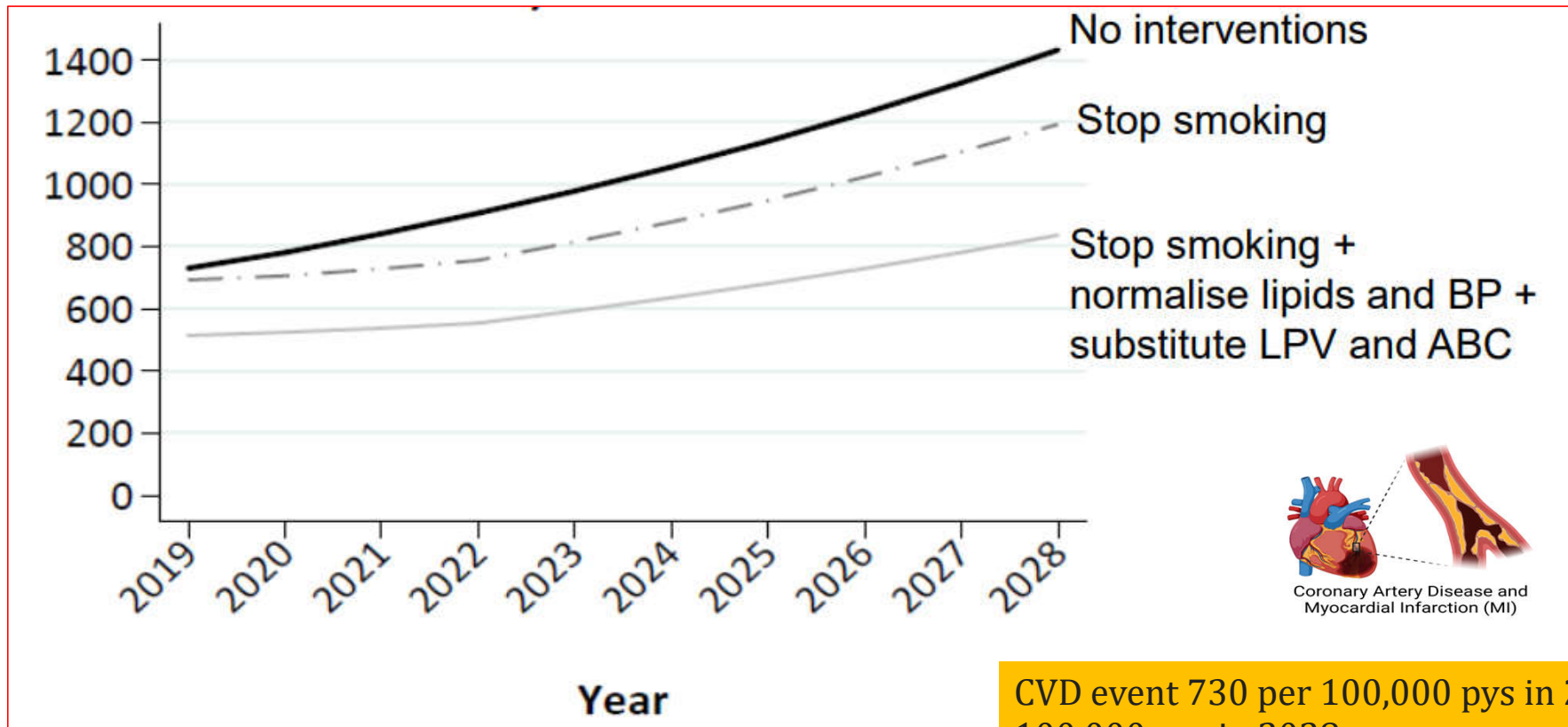
- Sex, HIV exposure category
- HIV viral load, CD4 count
- ART regimen
- HBV and HCV coinfection
- FPG, HDL cholesterol, smoking

Bijker et al. HIV Medicine 2019;20:183—191

Jung et al. JIAS 2019;22:e25219

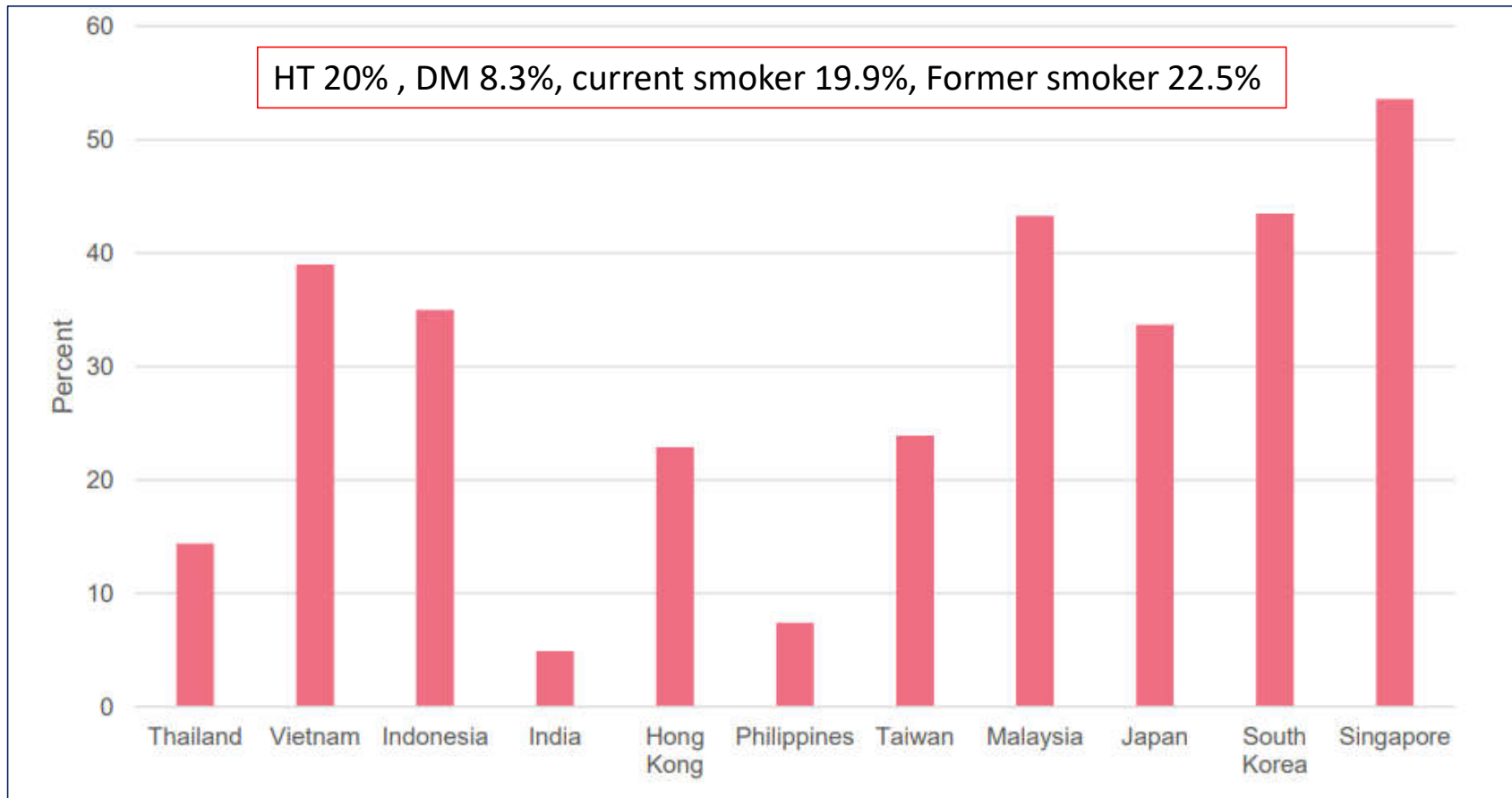
Cardiovascular disease incidence projections in the TREAT Asia HIV Observational Database (TAHOD) 2019-2028

N=3703, 69% =male, median age = 46 years, and median time ART duration = 9.8 years

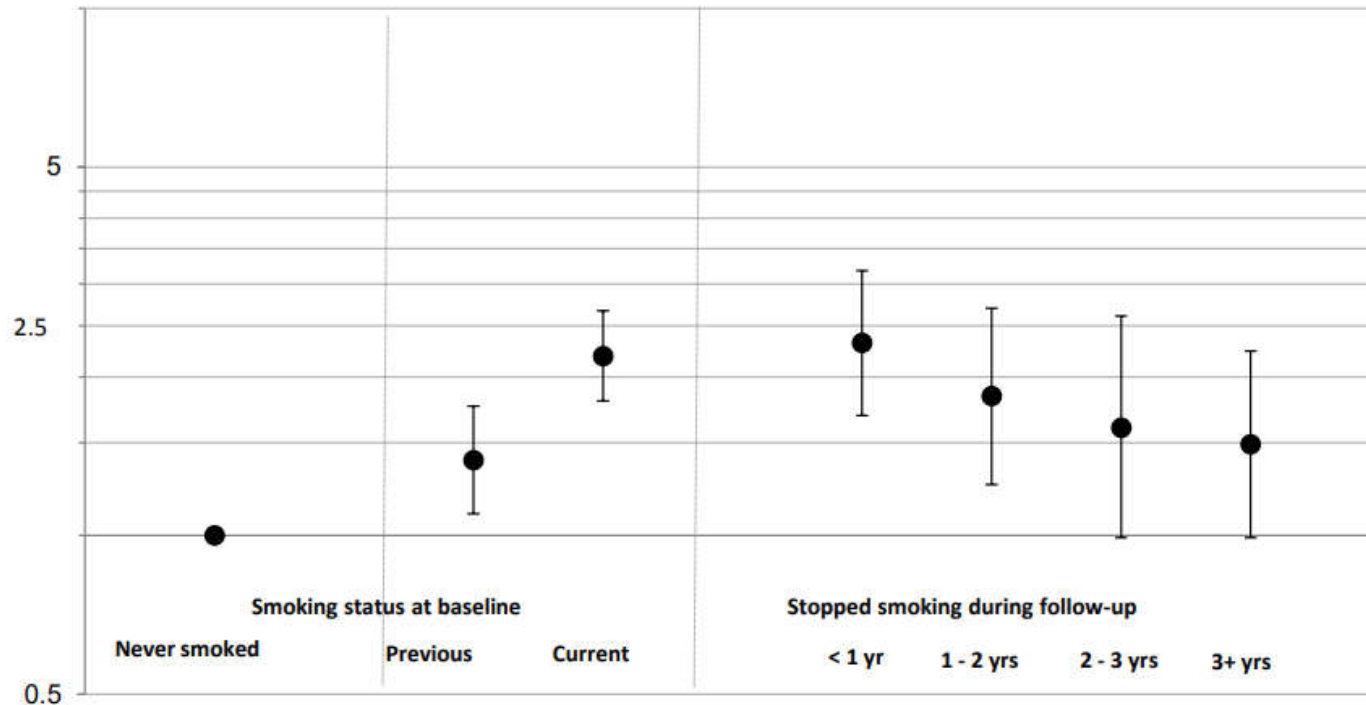


CVD event 730 per 100,000 pys in 2019 to 1432 per 100,000 pys in 2028

Smoking prevalence in TAHOD 2012-2013, N= 4274



↓ Risk of CVD following smoking cessation – D:A:D Study¹

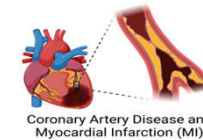


After quitting smoking:

- Heart rate and blood pressure drop after **20 minutes**².
- Heart attack drops significantly after **1 year**³.
- Risk of a stroke compares to that of a non-smoker after **2 to 5 years**⁴.
- Risk of coronary heart disease resembles that of a non-smoker's after **15 years**⁵.
- Quitting smoking before the age of **40 avoids more than 90% of the excess risk of death**⁶

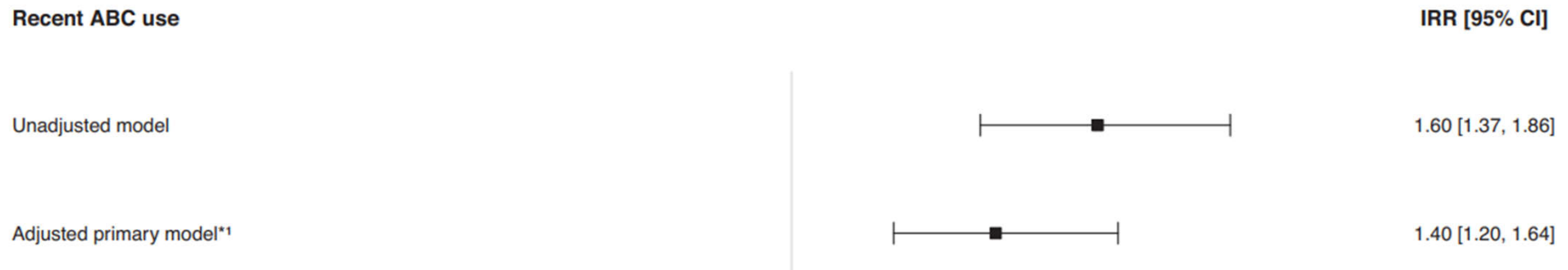
¹Petoumenos et al. HIV Medicine 2011;12(7):412-21; ² Mahmud A, Hypertension. 2003;41(1):183-187; ³. US Surgeon General's Report, 2010, p. 359; ⁴.US Surgeon General's Report, 2010 and World Health Organization IARC Handbooks of Cancer Prevention, Vol. 11. 2007, p. 341; ⁵ US Surgeon General's Report, 2010 and World Health Organization. IARC Handbooks of Cancer Prevention, Vol. 11. 2007, p. 11.;⁷ Jha, P. *eLife* **9**, e49979 (2020)

RESPOND: ABC and CVD Risk:



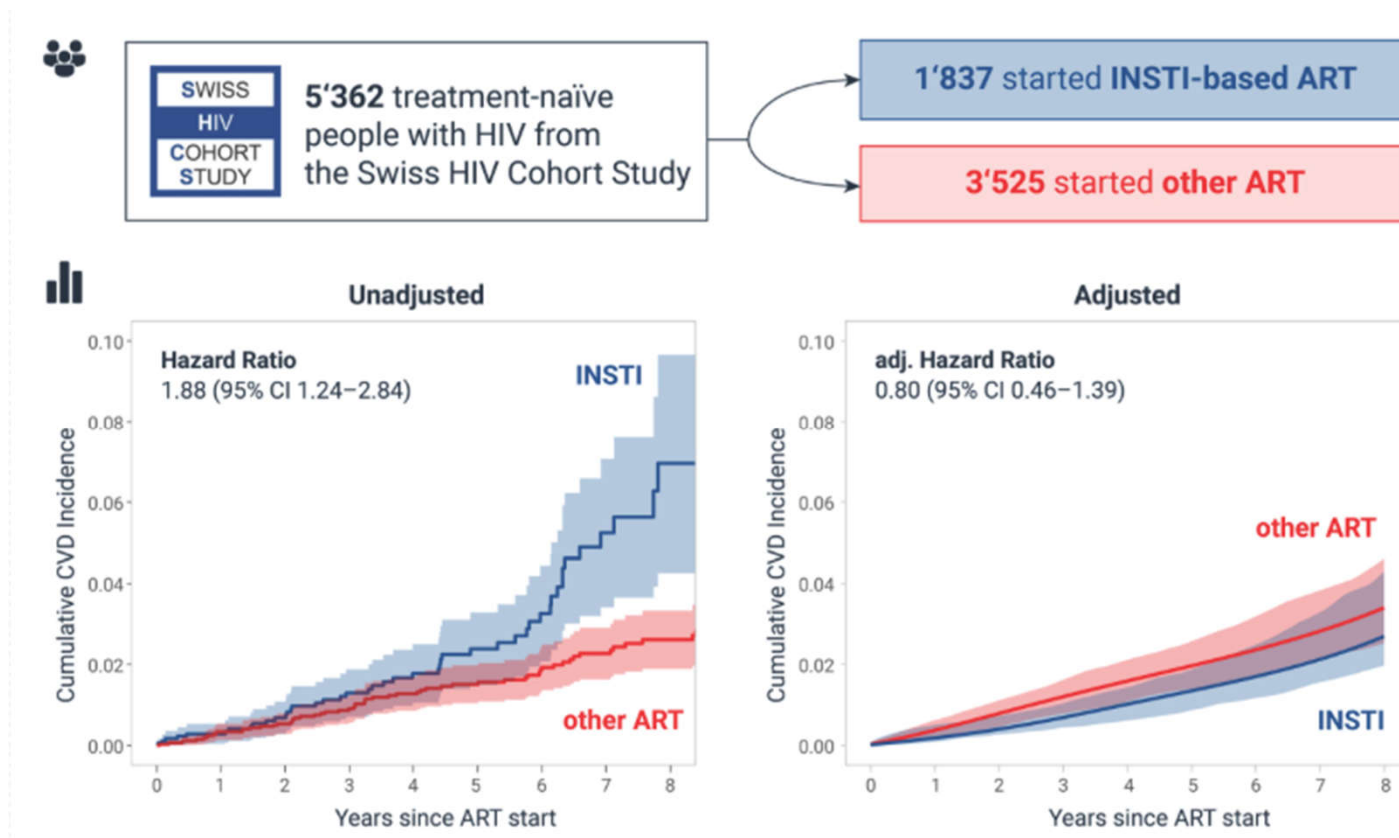
- International collaboration of 17 cohorts: 01/2012 to 12/2019
- Composite endpoint of **MI, stroke and invasive** cardiovascular procedure; adjudicated events
- N=29,340; 30% recently used ABC (within past 6 months)
- 748 CVD events, 4.7/1000 PY

Abacavir use and cardiovascular disease risk *Jaschinski et al.*



Recent ABC use associated with a 40% greater incidence of CVD

Incident CVD Rates Similar with ART Initiation with INSTIs vs. Non-INSTI



ARV naïve

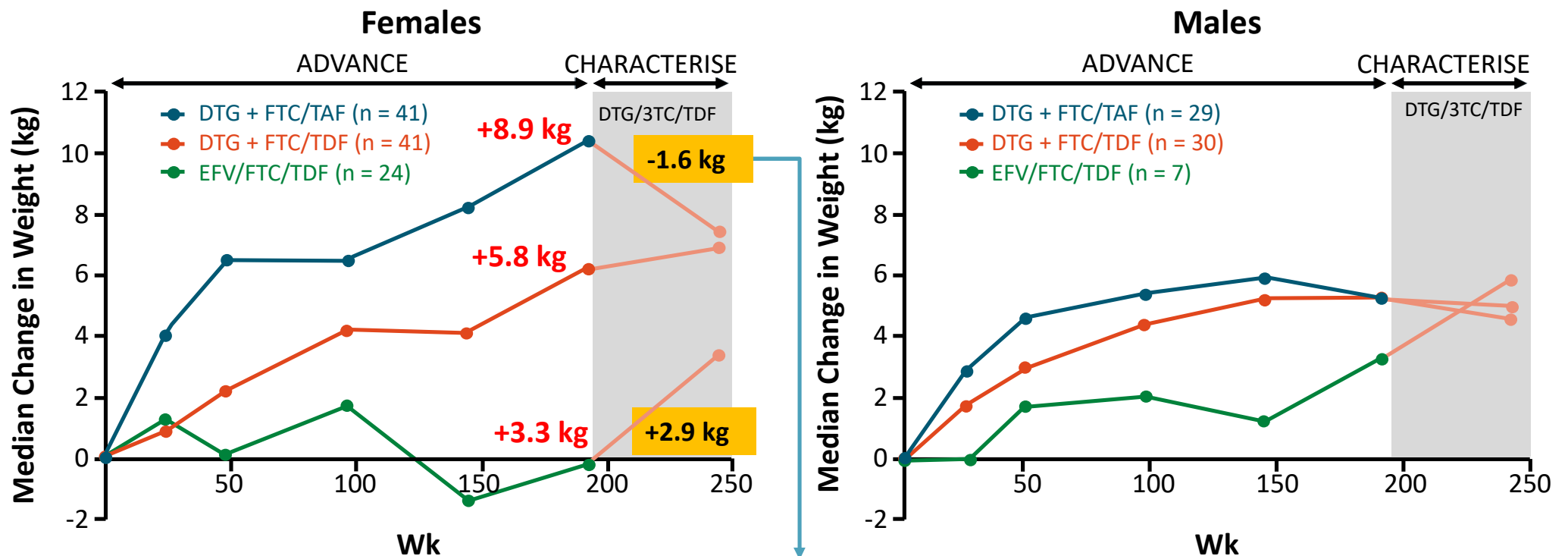
INSTI switched?

Median age: 39 years; Median BMI: 24; Nadir CD4: ~300, follow-up of 4.9 years (IQR, 2.4–7.4) : 116 events

Adjusted for calendar year, demographic & HIV variables, co-morbidities, use of antiplatelet and lipid-lowering drugs, current use of ABC and TAF

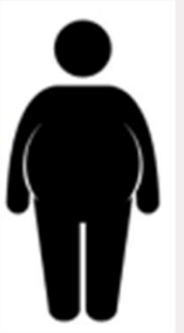
CHARACTERISE: Weight Change by Sex After Switch From ADVANCE Trial Regimens to DTG/3TC/TDF

CHARACTERISE: evaluation of weight and laboratory changes ≥52 wk after switch from ADVANCE trial to open-label DTG/3TC/TDF



In females, switch from DTG + FTC/TAF to DTG/3TC/TDF associated with median 1.6 kg weight loss

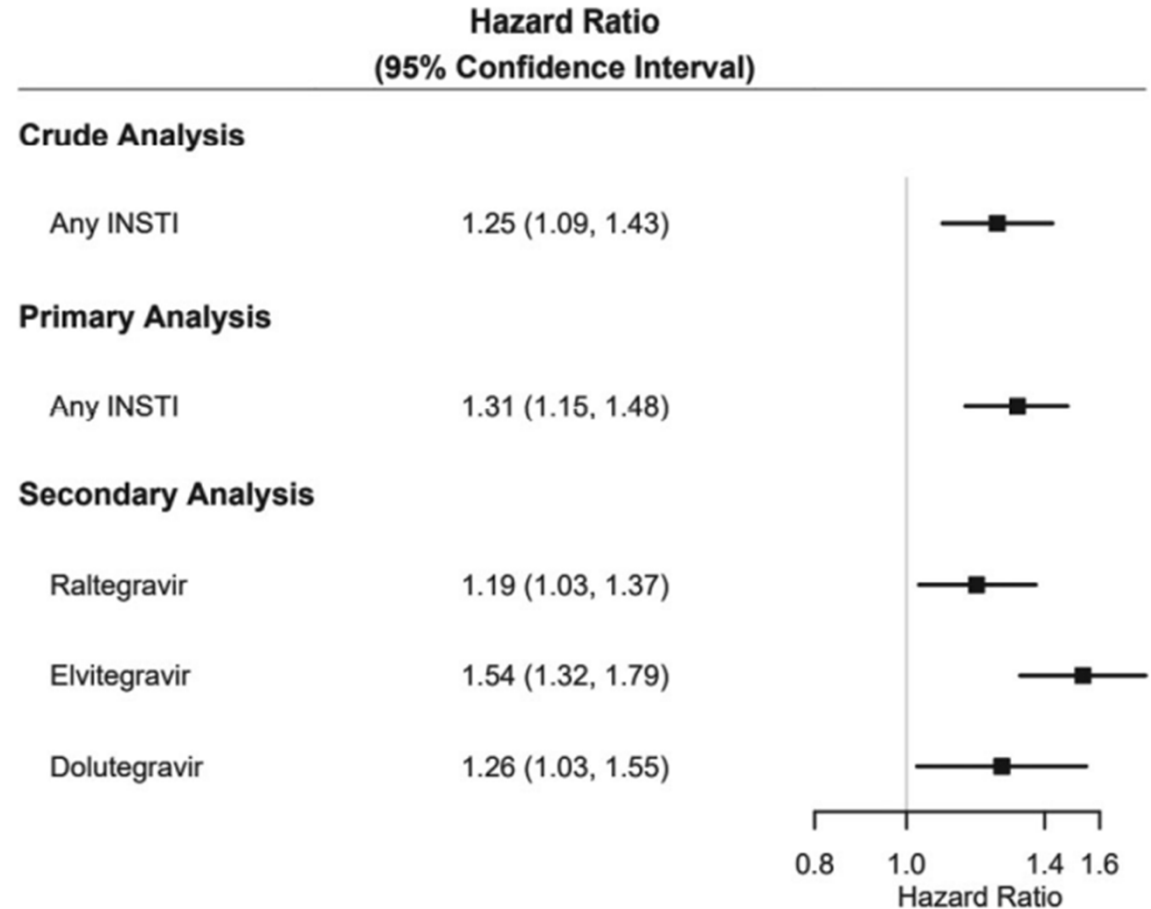
Obesity Risk in PWH Initiating INSTI or TAF: Analysis of 3 African Trials



Trial	Arm	Clinical obesity (probability)		
		Men	Women	Overall
ADVANCE (Week 192)	TAF/FTC/DTG	11%	42%	29%
	TDF/FTC/DTG	8%	28%	18%
	TDF/FTC/EFV	3%	20%	11%
NAMSAL (Week 192)	TDF/3TC/DTG	28%	25%	26%
	TDF/3TC/EFV	9%	20%	16%
VISEND BL<1,000 cp/mL (Week 96)	TAF/FTC/DTG	2%	22%	13%
	TDF/FTC/DTG	3%	14%	10%
VISEND BL≥1,000 cp/mL (Week 96)	TAF/FTC/DTG	6%	14%	11%
	TDF/FTC/DTG	1%	19%	12%
	ZDV/3TC/LPVr	4%	14%	11%
	ZDV/3TC/ATVr	7%	21%	15%

INSTIs Are Associated With Incident Diabetes Mellitus in PLWH

- Data from IBM MarketScan databases (2007-2018)
- Adults with commercial insurance and Medicaid on ARVs (N=43282, INSTI 54%, mean age 38 years, 74% male)
- Outcomes ascertained by ICD and CPT codes
- HR for new-onset DM/Hyperglycemia in PWH initiating ART ('07 to '19)
- **31% of INSTI developed new-onset diabetes mellitus/hyperglycemia**
- Bictegravir: HR: 1.45 (0.84–2.51; P = .182)
- Sensitivity analysis with TAF: HR: 1.28 (0.99–1.64; P = .06)
 - <5% were on concurrent TAF

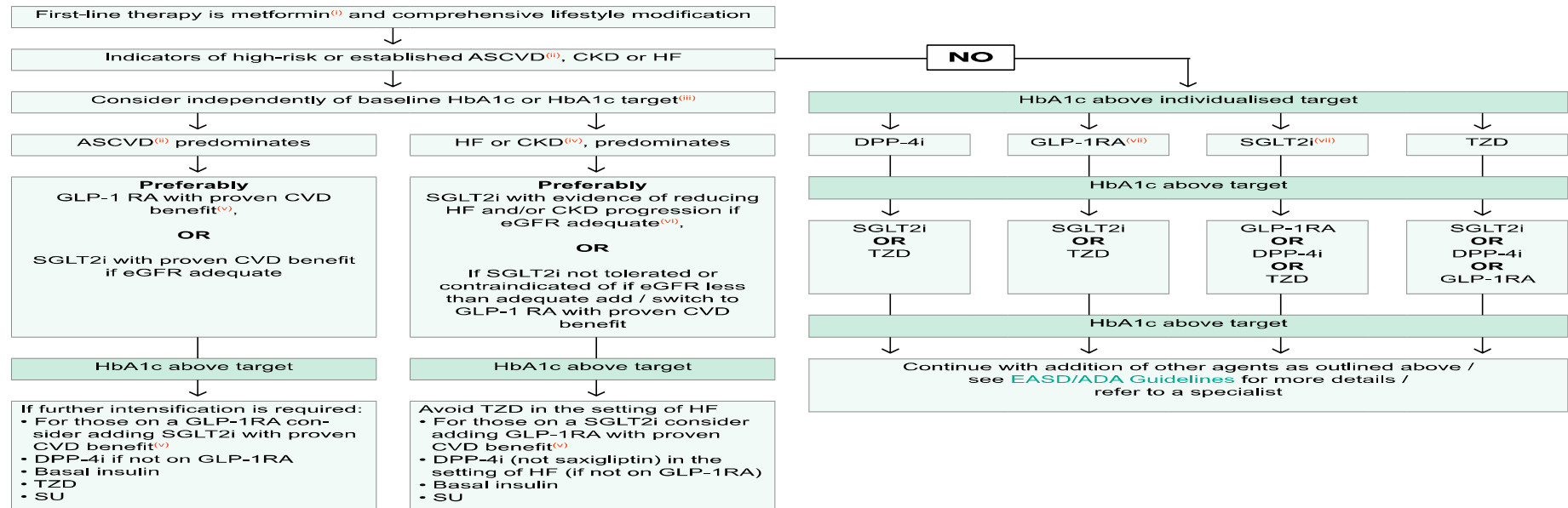


Adjusted for age, male gender, Elixhauser co-morbidities, gestational diabetes, pancreatitis, pancreatitis malignancy, Hepatitis B & C, cardiovascular disease, hypoglycemia

Management of Diabetes in PLWH

- Moderate intensity aerobic exercise *plus* nutritional optimization
- No evidence for ARV switch
- Metformin is the first-line medication recommended by the ADA, if there is no contraindication:
- ≥ 150 min of moderate intensity aerobic exercise over ≥ 3 days a week¹
- Calorie guideline options for weight loss.^{2,3}
 1. 1200–1500 calories/day for women or 1500–1800 calories/day for men
 2. An energy deficit of 500-750 calories per day
 3. An evidence-based diet that restricts a certain food type (e.g., high-carbohydrate foods) to create an energy deficit
- **IAS-USA: Yearly diabetes screening and assessment of cardiovascular risk score of patients receiving InSTI-based ART is recommended (evidence rating: BIII)⁴**
 1. ADA. Diabetes Care. 2020;43(Suppl 1):S48-s65; 2. Knowler et al, NEJM, 2002; 3. Monroe et al, CID, 2014
 4. Gandhi. JAMA. Published online December 1, 2022. doi:10.1001/jama.2022.22246

Type 2 Diabetes: Management



- i** Metformin may worsen lipoatrophy. Consider lower dose in persons with HIV with mild to moderate CKD or in individuals receiving DTG
- ii** Established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD (age \geq 55 years + left ventricular hypertrophy or coronary, carotid, lower extremity artery stenosis $>$ 50%)
- iii** No data for any oral anti-diabetic agents in terms of CVD prevention in persons with HIV. Choice of drugs dependent on a variety of individual- & disease-specific factors; no clinically significant drug-drug-interaction or adverse effects on CD4 counts expected. Always consider individualised HbA1c targets, which depend on e.g. disease duration, life expectancy, risk for hypoglycemia, individual preference
- iv** Heart failure (HF) defined as reduced ejection fraction $<$ 45%, chronic kidney disease (CKD): eGFR $>$ 30 - $<$ 60 mL/min or UA/C $>$ 30 mg/mmolL, particularly UA/C $>$ 300 mg/mmolL
- v** Proven CVD benefit means it has label indication of reducing CVD events
- vi** Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression
- vii** Compelling need to minimise weight gain or promote weight loss use GLP-1RA or SGLT2i. GLP-1RA with good efficacy for weight loss: semaglutide $>$ liraglutide $>$ dulaglutide $>$ exenatide $>$ lixisenatide

Weight Gain and Obesity is associated with diabetes mellitus

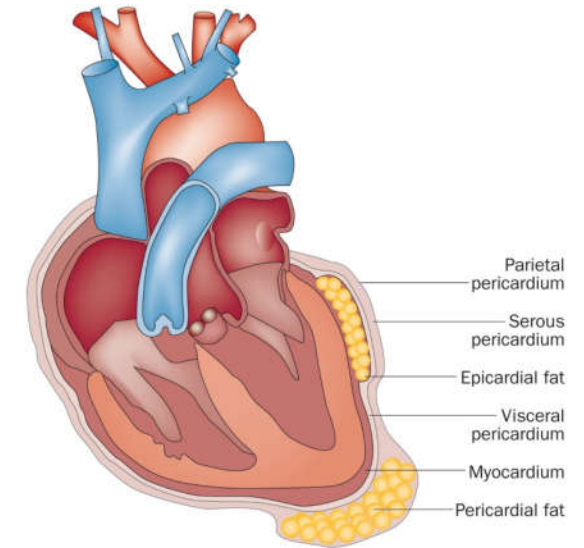
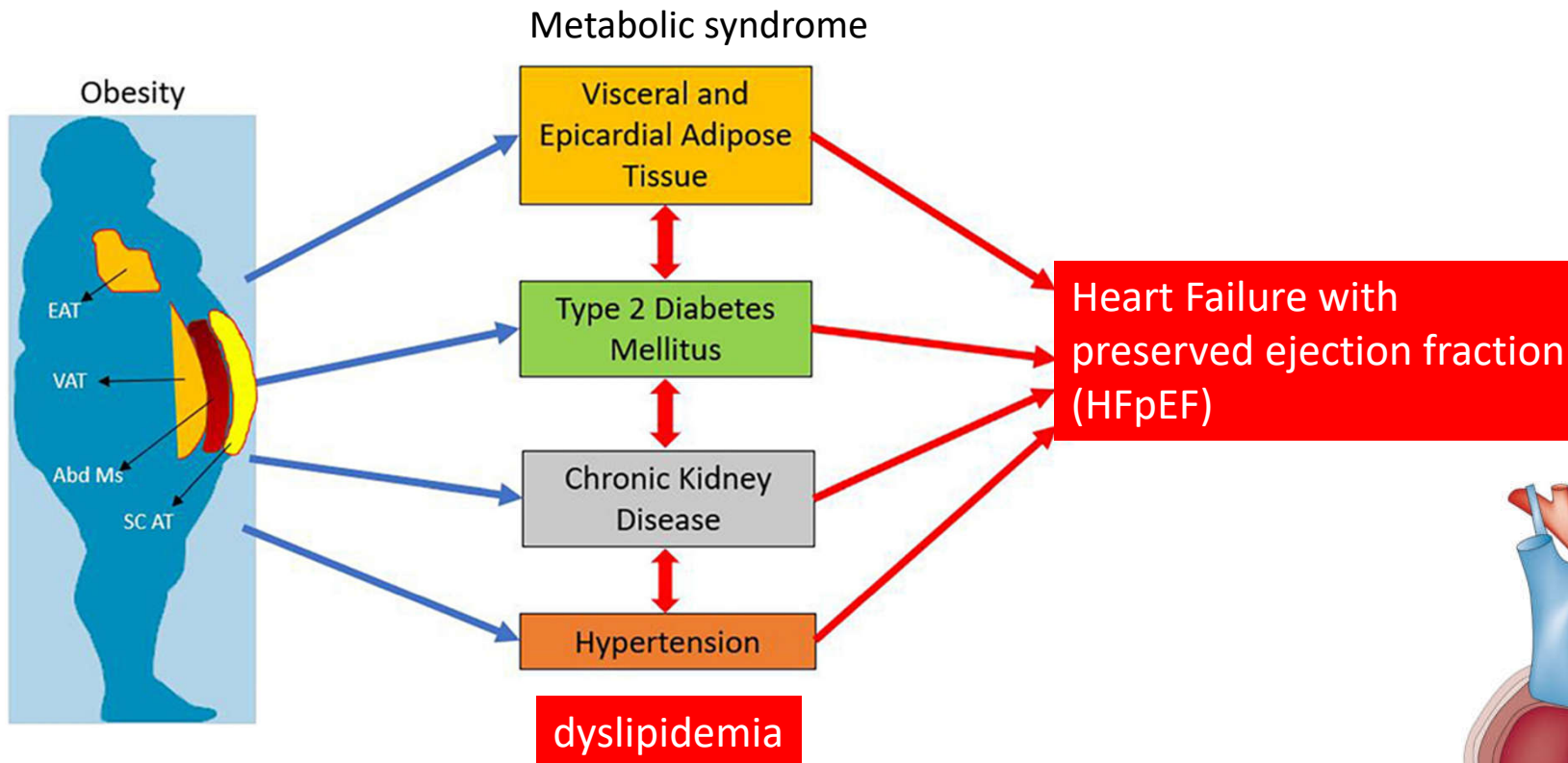
- BMI as a predictor of high fasting blood glucose among PLWH in the Asia-Pacific region¹
 - N=3939 (63% male, median age at ART= 34 yrs), 13% were overweight, and 14% were obese, 8% had a high FBG.
 - BMI ≥ 25 kg/m² increased risk of high FBG (HR= 1.79; 95% CI 1.31–2.44)

- Diabetes mellitus burden among PLWH in the Asia-Pacific region²
 - N=1927, median ART to DM diagnosed was 5.9 yrs; 127 were diagnosed DM (6%) after ART initiation
 - BMI > 30 kg/m² increased risk of DM(HR= 4.3; 95% CI 1.53–12.09)

New-onset Diabetes mellitus burden among PLWH in Thailand³

- N=1748, median ART duration was 9 yrs; 123 were diagnosed DM (7.6%) after ART initiation
- BMI ≥ 25 kg/m² increased risk of DM(HR= 2.66; 95% CI 1.7–14.6)
- Diabetes increased risk of CVD (8.9% vs 3.6%, CKD : eGFR < 60 ml/min/1.73m² (15.3% vs 1.9%)

Weight Gain and obesity increased epicardial fat?



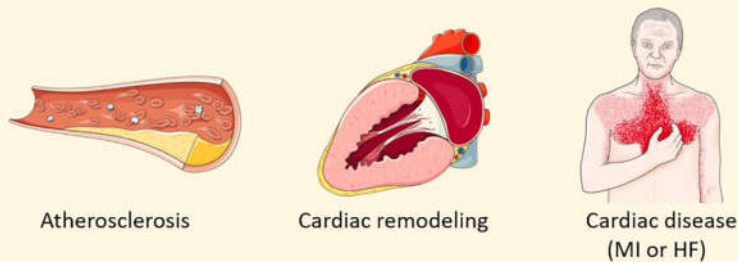
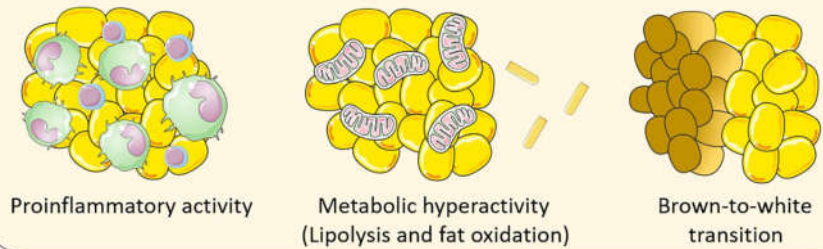
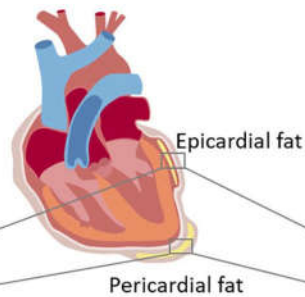
Dhore-patil A Front. Physiol., 15 February 2022

Increased Epicardial Fat

Lo J. AIDS 2010; 24: 2127-30. Brener M. AIDS. 2014; 28: 1635-44. Srinivasa S.. Antivir Ther. 2018, 23: 1-9. Packer M. JACC. 2018; 71:2360-72.

Weight Gain and obesity increased epicardial fat and heart failure?

Epicardial Fat Expansion in Diabetic and Obese Patients With Heart Failure and Preserved Ejection Fraction¹



- Epicardial fat is associated with abnormal haemodynamics, cardiac fibrosis and heart failure with preserved ejection fraction (HFpEF)
- Contributes to atherogenesis, Cytokine production
Activated macrophages
- Increased in HIV
Matched for age, race, BMI

Higher epicardial fat in older adults PLWH in Thailand (compared to age, gender match HIV neg)
 -Associated with coronary calcium score and severe liver fibrosis
 -Duration of ART was significantly associated with higher EAT

Elsanhoury A Front. Cardiovasc. Med., 17 September 2021; LO J. AIDS 2010; 24: 2127-30.

Brener M. AIDS. 2014; 28: 1635-44.

Srinivasa S.. Antivir Ther. 2018, 23: 1-9. Packer M. JACC. 2018; 71:2360-72; Tumkosit M AIDS 2022;36(8):1073-1081.

Inflammation Persists in the Setting of Treated HIV Infection; VL and CD4 assoc. with AMI risk

- T-cell activation higher in treated HIV vs controls^[1]
- LPS higher in treated HIV vs controls^[2]
- Tissue factor elevated in treated HIV vs controls^[3]

HIV RNA \geq 500 and CD4 $<$ 200 each associated with increased AMI risk
 AMI risk persists in patients achieving viral suppression or immune reconstitution^[4]

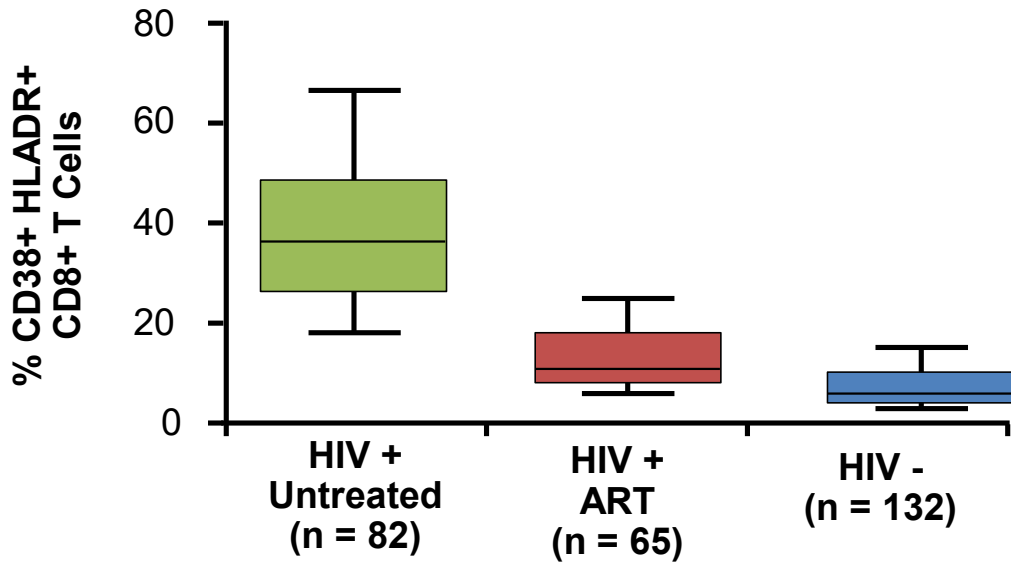
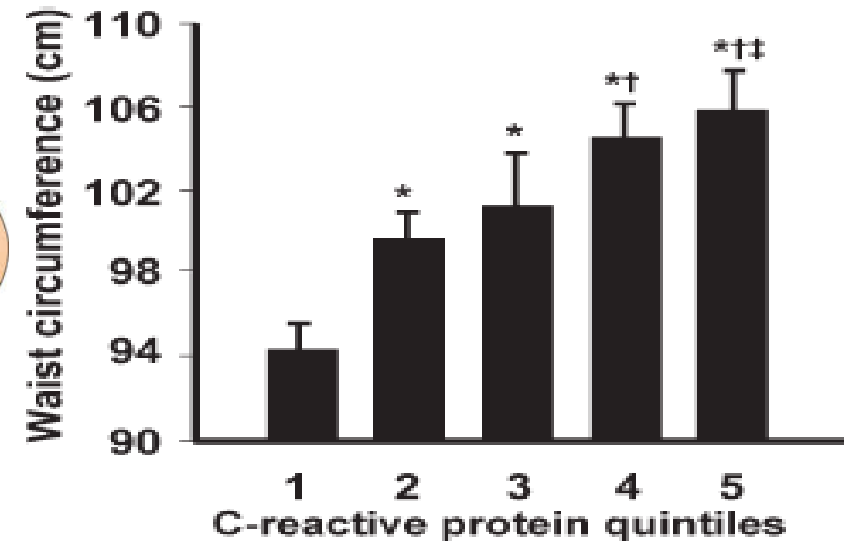
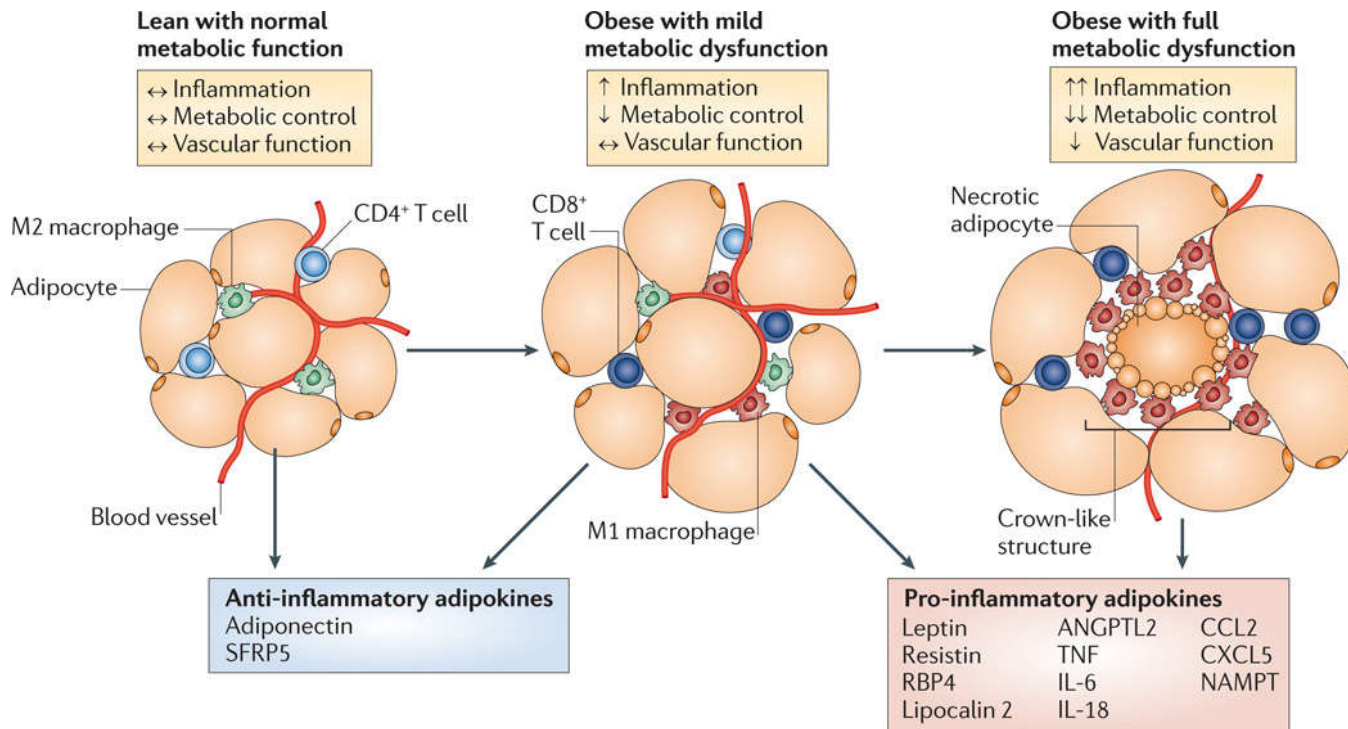


Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models^a

Category	HR (95% CI)	P Value ^b
HIV-1 RNA		
Uninfected	1 [Reference]	.05
\geq 500	1.75 (1.40-2.18)	
$<$ 500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	.04
$<$ 200	1.88 (1.46-2.40)	
\geq 200	1.43 (1.21-1.69)	

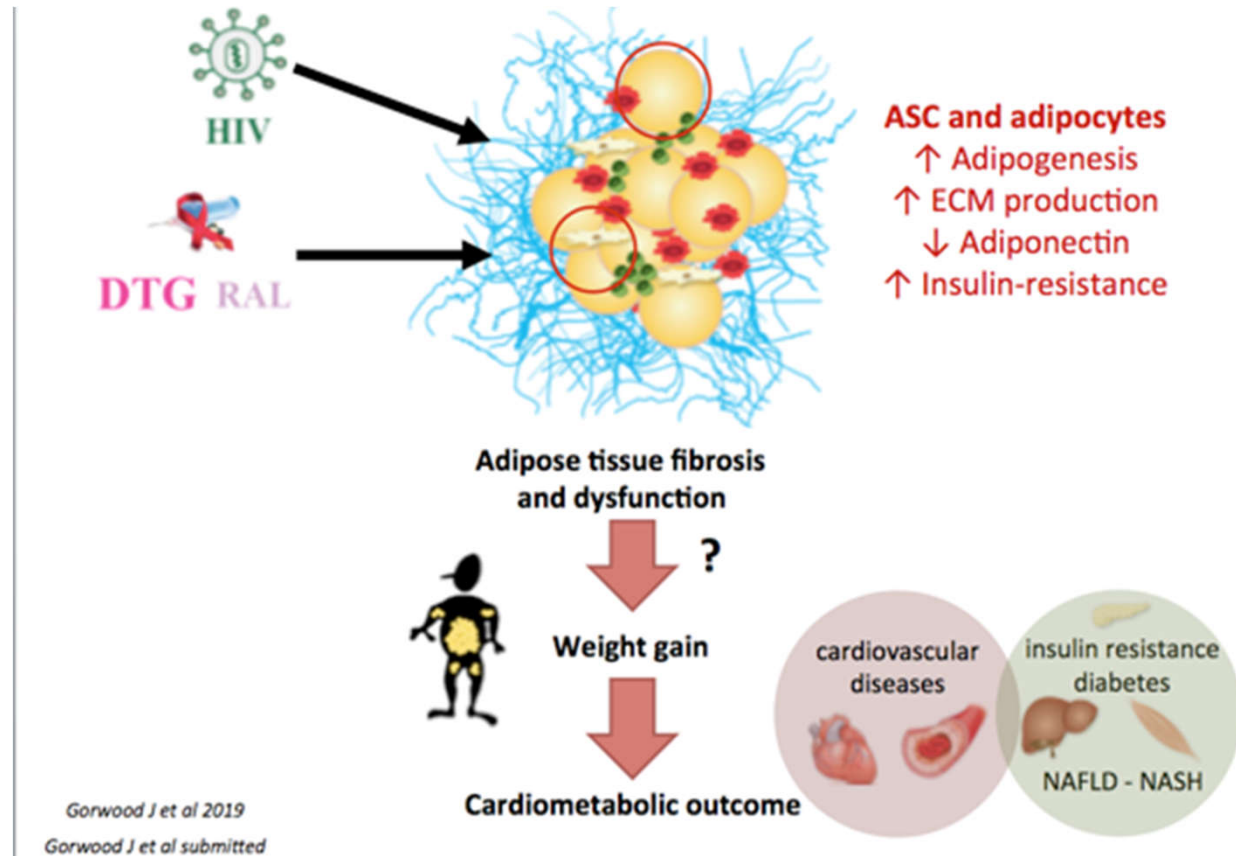
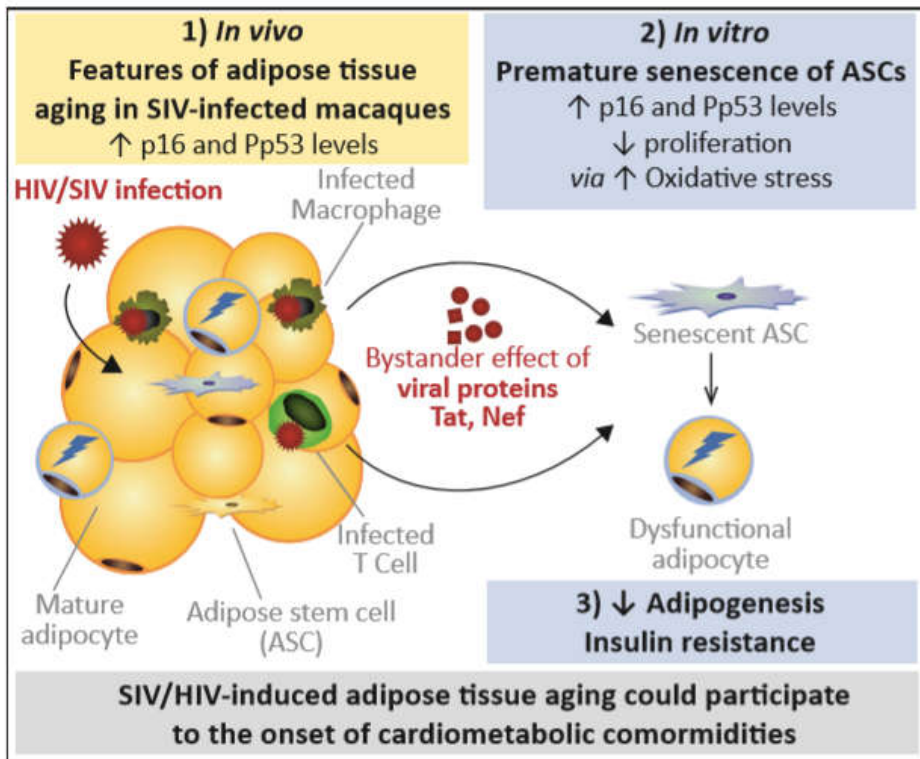
1. Hunt PW, et al. J Infect Dis. 2003;187:1534-1543. 2. Brechley JM, et al. Nat Med. 2006;12:1365-1371.
 3. Funderburg NT, et al. Blood. 2010;115:161-167.; 4. Freiberg. JAMA Intern Med. 2013

Obesity-Induced Inflammatory Changes in Adipose Tissue – Phenotypic Modulation



Samaras K et al. Obesity 2008;17:53-59

HIV Induces Adipocyte Dysfunction; Likely worsened by Integrase Inhibitors



Cells 2020, 9(4), 854; <https://doi.org/10.3390/cells9040854>; 2. J Antimicrob Chemother. 2021 Jun13;dkab158. doi: 10.1093

NAFLD, NASH, Cirrhosis More Prevalent in PWH

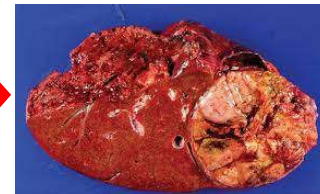
NAFLD

Cancer : Colon ,
CVDs
Metabolic syndrome
Diabetes
hypertension

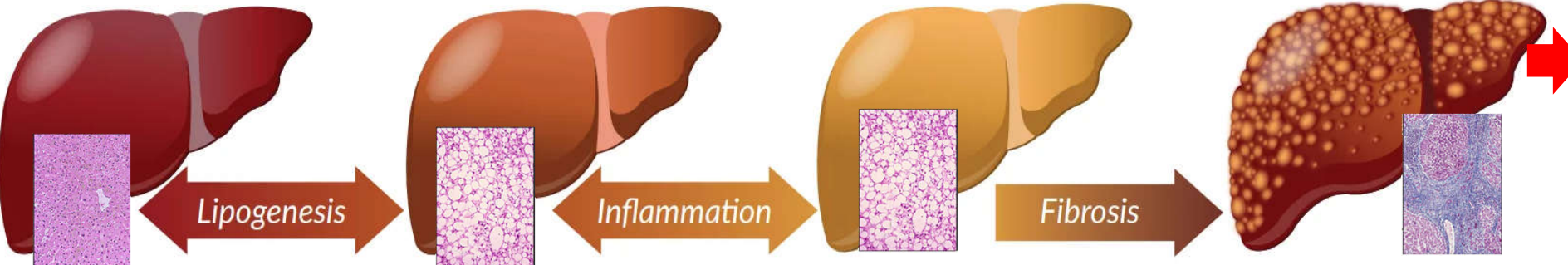
Steatosis
"NAFL"

Steatohepatitis
"NASH"

Cirrhosis



HCC



Worldwide prevalence: 25%^{1,2} 3% to 5%¹ 1% to 2% at risk*

Prevalence in HIV: 13% to 65%² 10%³ 2.3-6% at risk²

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis.⁴

MAFLD Caused by overweight/obesity, diabetes mellitus, or ≥2 **metabolic risk abnormalities**

1. Younossi. J Hepatol. 2019;70:531. 2. Cervo. Curr HIV/AIDS Rep. 2020;17:601.
3. Benmassaoud. PLoS ONE. 2018;13:e0191985. 4. Kabbany. Am J Hepatol. 2017;112:581.

REPRIEVE (A5332): Pitavastatin or a placebo to reduce CVD in low to moderate risk

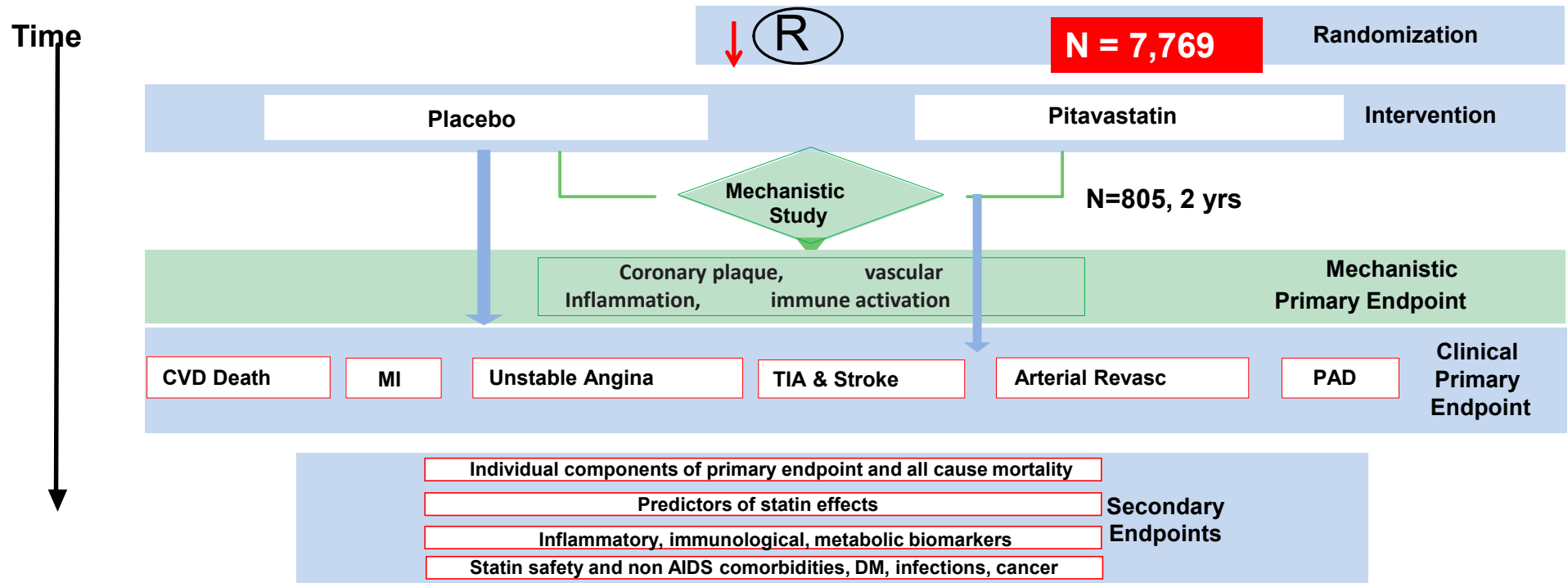
- Atherosclerosis is inflammatory; HIV pts have vascular inflammation
 - Asymptomatic HIV patients have ↑ plaque
 - HIV patients: 2x ↑ risk for CVD despite low traditional risk profile
- What are the characteristics of an ideal treatment for HIV patients?
 - Traditional effect of lowering LDL
 - Pleiotropic effects to reduce monocyte activation, chemoattraction and vascular inflammation
 - Safe and well tolerated in HIV population; Few drug interactions
- Current use is low among HIV patients (19.6% in ACTG)



REPRIEVE (A5332): Pitavastatin or a placebo to reduce CVD in low to moderate risk

HIV-NAT = 412

Asymptomatic PLWH, 10-year ASCVD risk $\leq 15\%$, age 40-75 years, on ART > 6 months, CD4 > 100, LDL < 190 mg/dl, TG < 500 mg/dl, ALT ≤ 2.5 ULN, CrCl > 60 ml/min; LDL < 70 mg/dl if DM, FIB 4 ≤ 3.25 if HBV, HCV



COVID 19 infection/vaccines

Exclusion : Known CVDs, Active cancer within 3 years, Cirrhosis, History of myositis/myopathy within 6 months, Exclusionary meds and other conditions

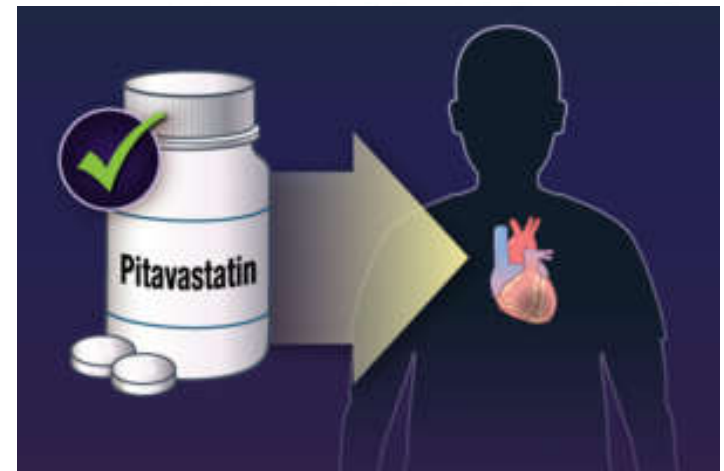
Statins and the Risk of ASCVD in PWH

- 7,769 PWH: 40 to 75 years :Low - moderate ASCVD Risk.
- Median age was 50 years, 31% were female (natal sex), 43% black or African American and **15% Asian**, Median BMI 25.8,
- Randomly assigned to 4 mg of pitavastatin qd or placebo
- Stopped by DSMB for efficacy: 35% reduction of MACE

NHLBI NEWS | News Release

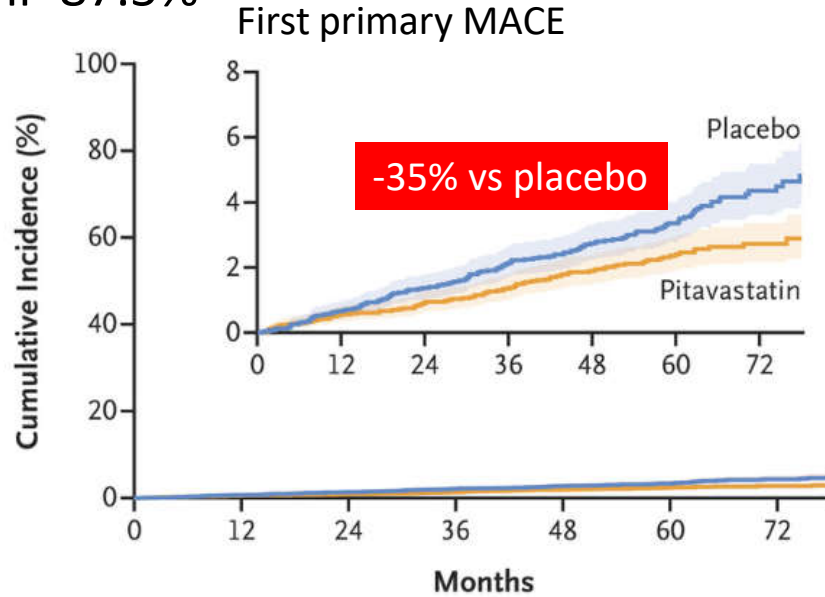
Daily statin reduces the risk of cardiovascular disease in people living with HIV, large NIH study finds

April 11, 2023, 2:00 PM EDT

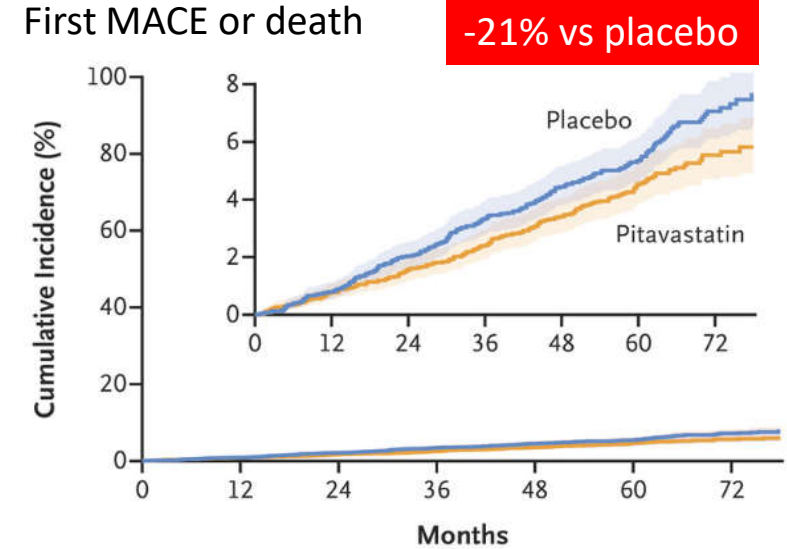


Median age 50 years, female 31.1%, Asian 14.7%, Black 41.3%, White 31.8%, Hispanic 17.8%, median ASCVD 4.5% (2.1-7), 49% Nadir CD4 < 200 cells/mm³, 32% baseline CD4 < 500, HIV RNA < 50 c/ml=87.5%

High income : 52.7%
 Latin America: 18.3%
 Southeast or East Asia: 7.6%
 South Asia: 6.5%
 Sub-Saharan Africa: 14.9%



	0	12	24	36	48	60	72
Placebo	0.00	0.66	1.38	2.14	2.74	3.36	4.36
Pitavastatin	0.00	0.56	0.95	1.35	1.89	2.41	2.73



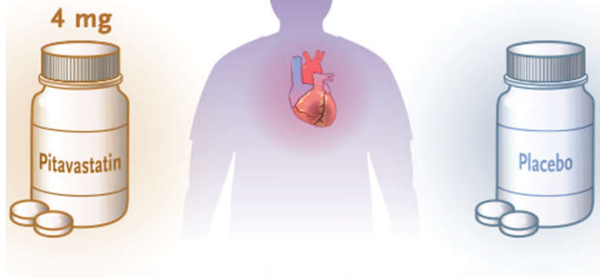
	0	12	24	36	48	60	72
Placebo	0.00	0.80	2.03	3.34	4.44	5.35	7.06
Pitavastatin	0.00	0.77	1.58	2.39	3.40	4.54	5.54

Adverse event related discontinuation was low in each group : 2% vs 1% pitavastatin vs placebo
 Clinical initiation of a non-study statin occurred in 5.7% pitavastatin vs 9.6% of placebo

REPRIEVE (A5332): Pitavastatin or a placebo to reduce CVD in low to moderate risk

N=3888

N=3881

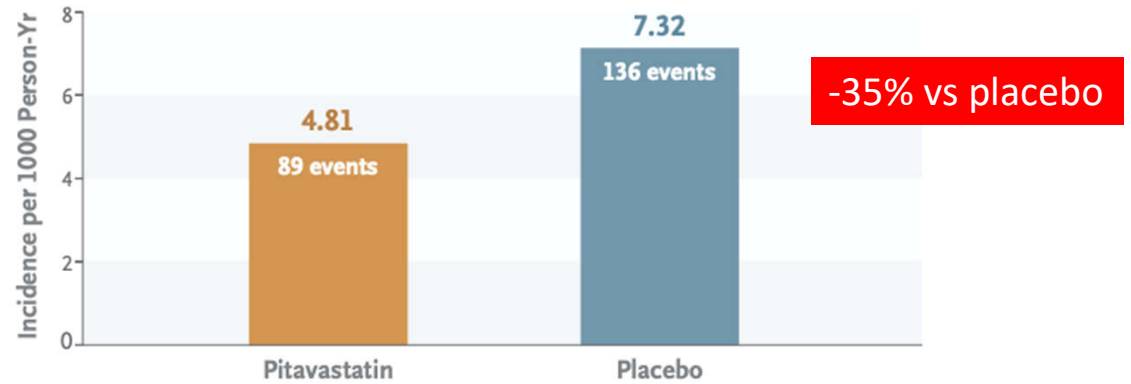


CONCLUSIONS

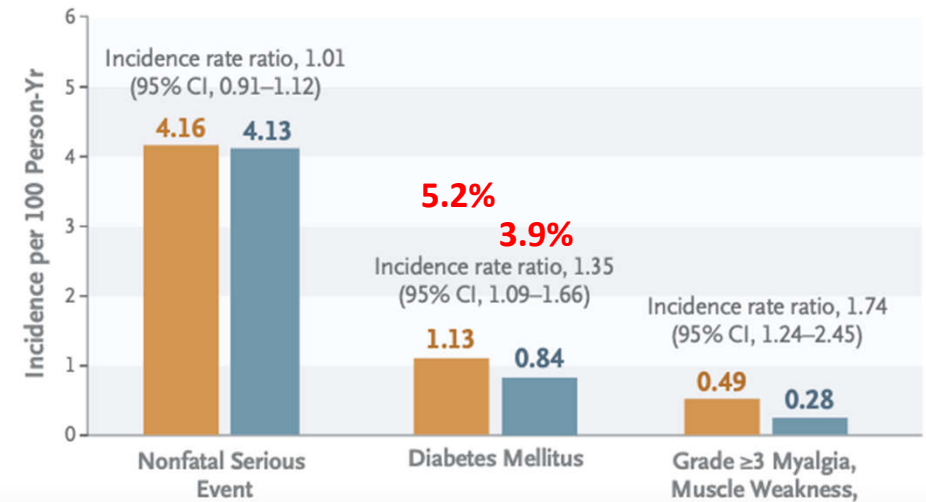
In persons with HIV infection receiving stable antiretroviral therapy and at low-to-moderate cardiovascular risk, daily treatment with pitavastatin resulted in a significantly lower risk of major adverse cardiovascular events than placebo over approximately 5 years of follow-up.

Major Adverse Cardiovascular Events

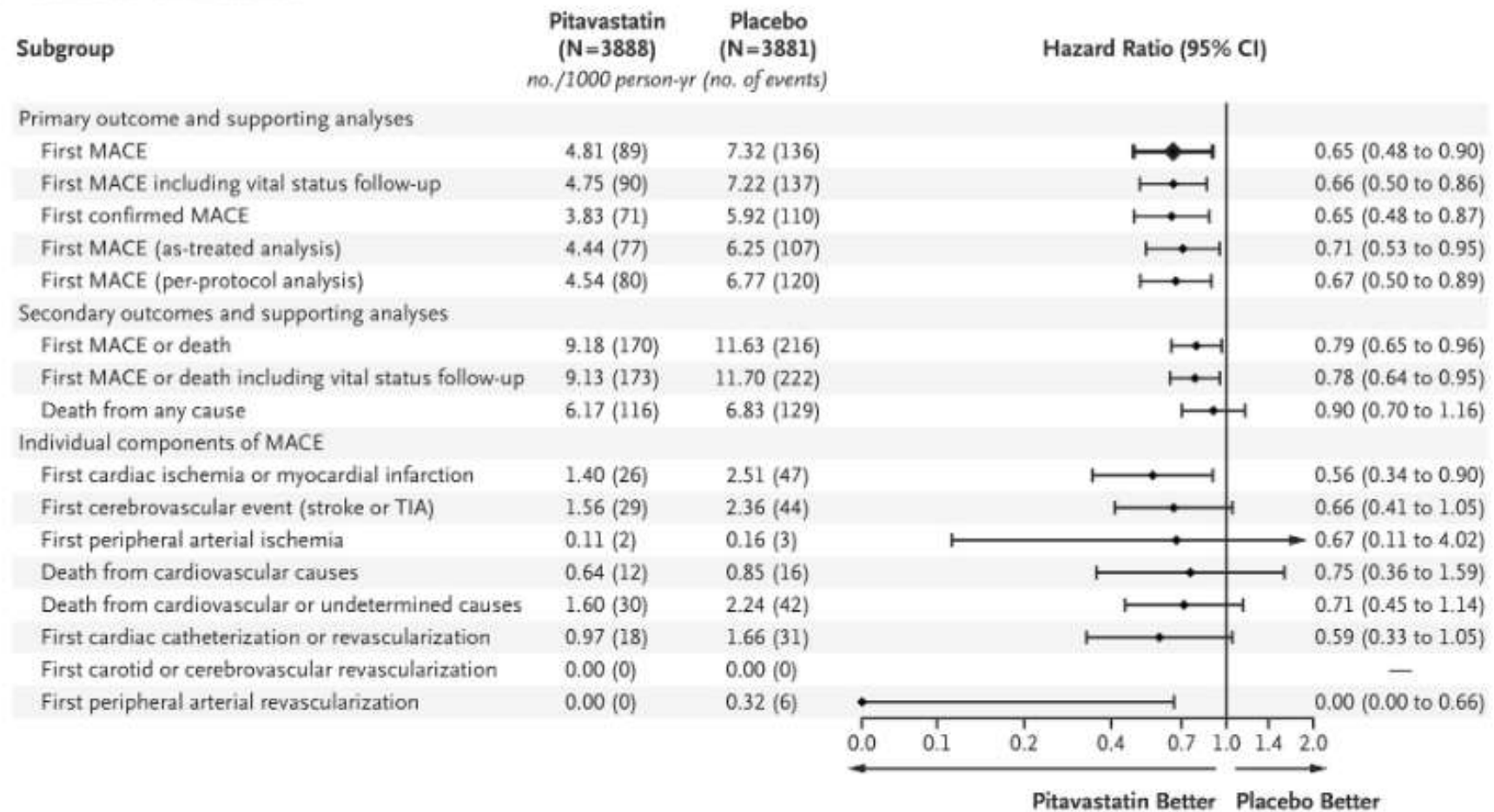
HR, 0.65 (95% CI, 0.48–0.90); P=0.002

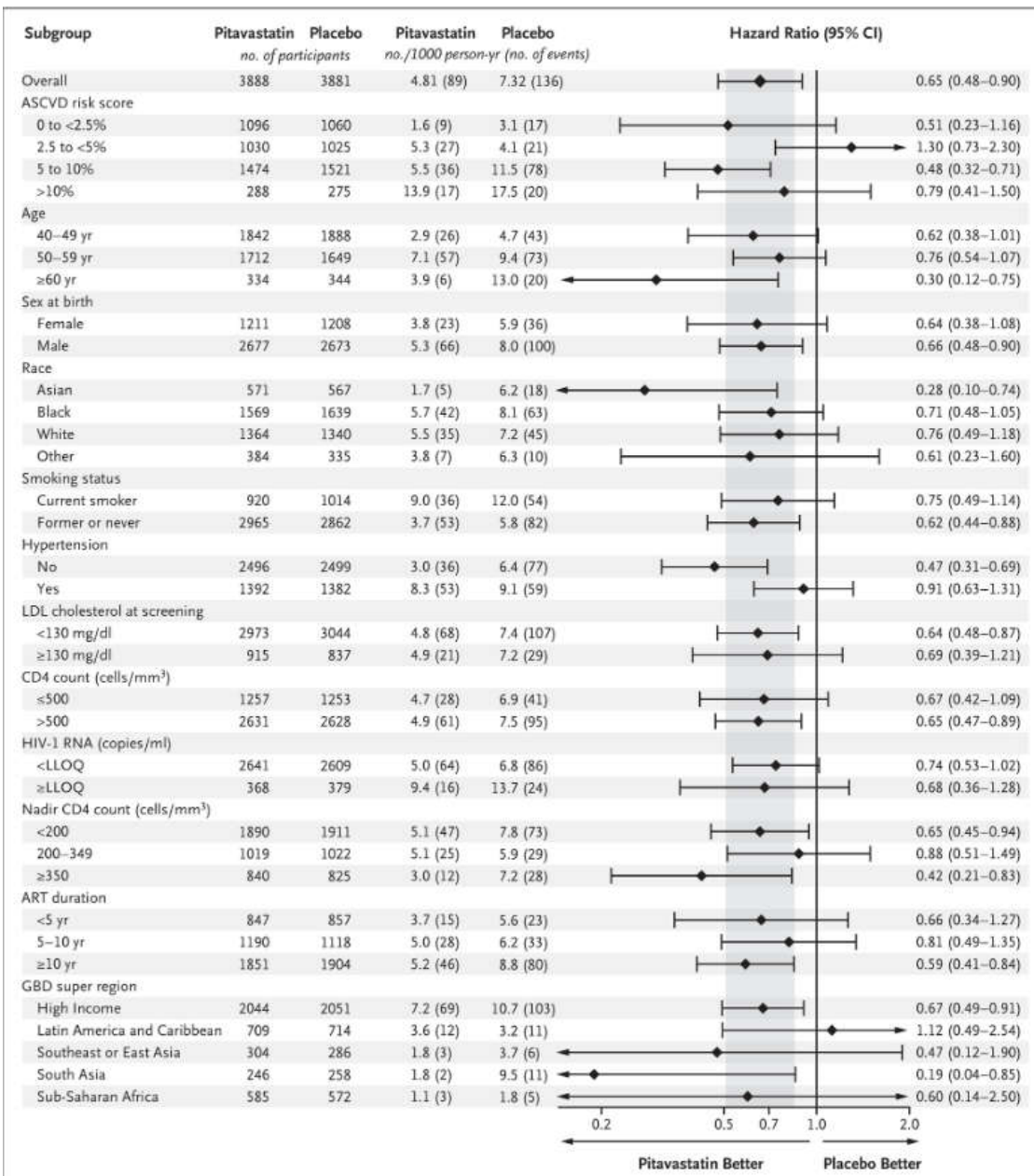


Adverse Events



Estimate treatment effect





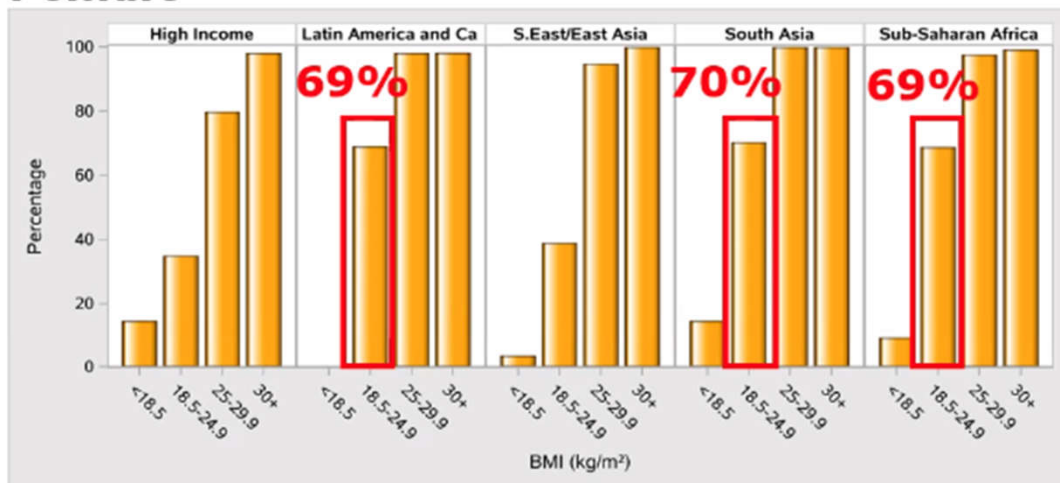
Effects on Key subgroups

- Very consistent effect across major subgroups
- No treatment modification based on screening LDL, age, sex
- Generally consistent effects across race and GBD regions
- No treatment modification based on CD4, nadir CD4, HIV RNA, ART duration

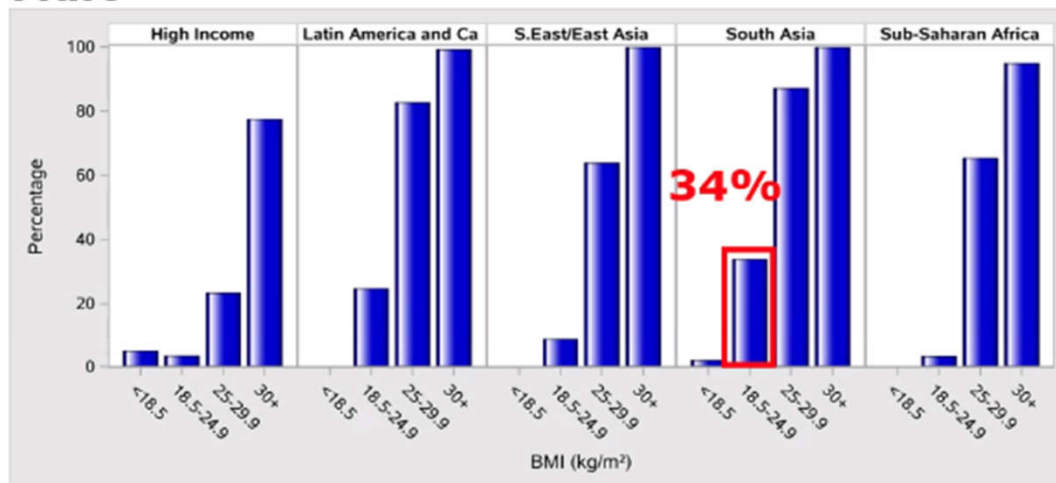
GBD=global burden of disease

Baseline High Waist Circumference by BMI, Sex, Region in REPRIEVE

Female



Male



- Higher WC despite normal BMI in LAC, S Asia, SSA, (+ S Asia males)
- Largest MACE effect size seen in S Asia, SE/E Asia

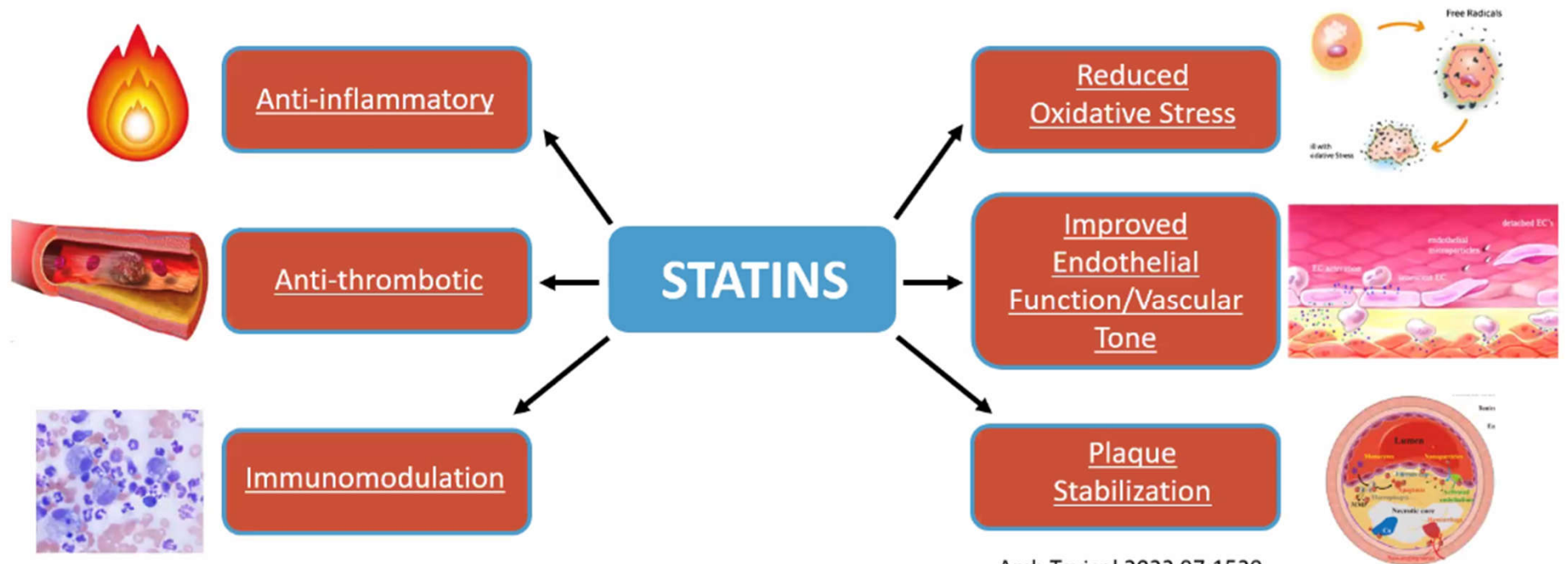
Regional variation in metabolic dysregulation, visceral adiposity despite 'normal' BMI driving CV risk

* Women: ≥88 cm in US, ≥80 cm for all other regions. Men: ≥102 cm in US, ≥90 cm in LAC and Asia, ≥94cm for all other regions.



Beyond LDL: Pleiotropic Effects of Statins

Statins primary effect is to inhibit HMG-CoA reductase to lower LDL cholesterol
Statins have many other beneficial effects to reduce vascular disease

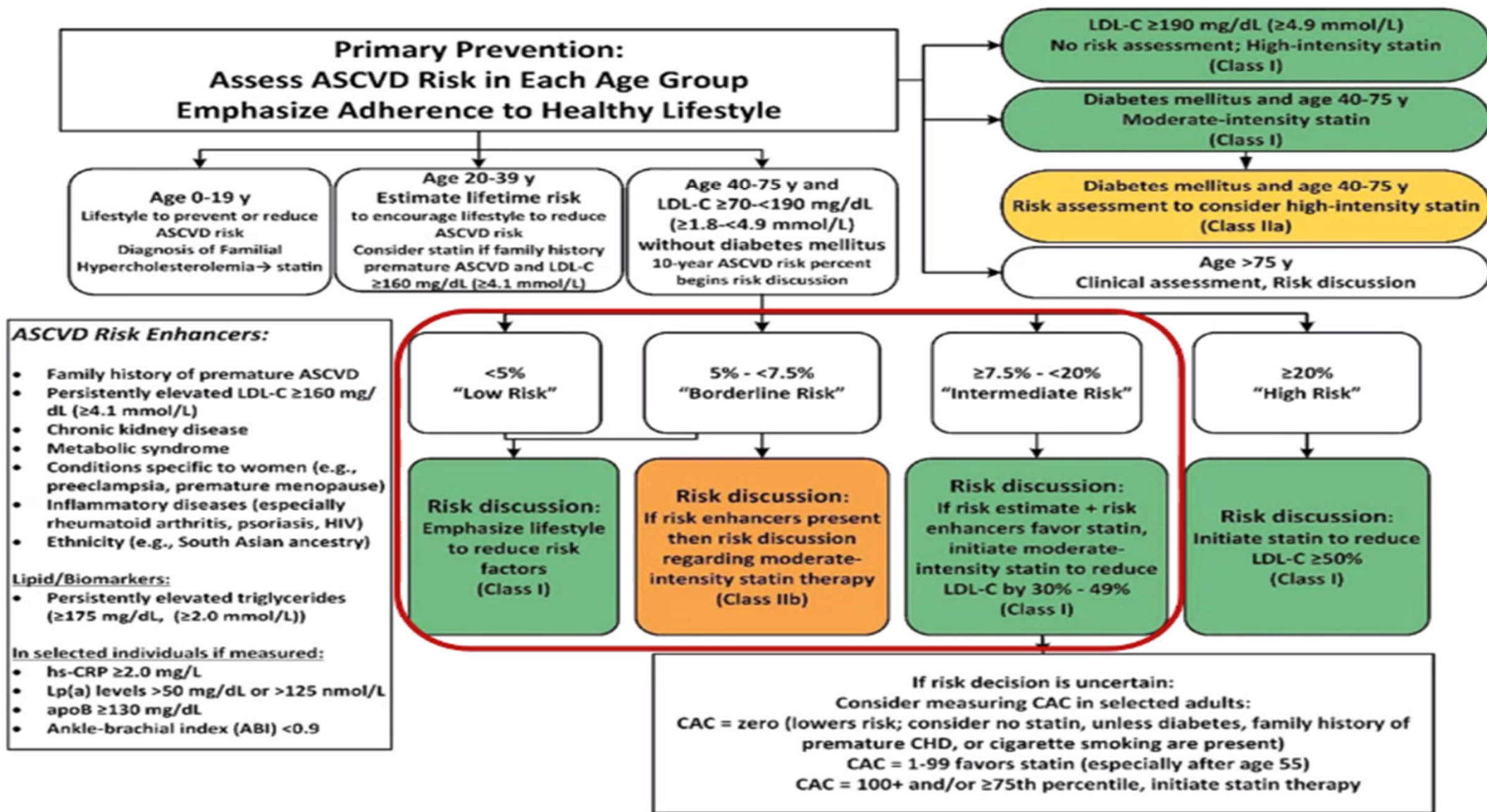


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Management of dyslipidemia

- ✓ **Principles:** Higher LDL-c levels increase risk of CVD and reduction diminishes this risk.
- ✓ TG: < 1.7 mmol/L (< 150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
- ✓ Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridemia [TG > 2.3 mmol/L (> 200 mg/dL)].
- ✓ Very high TG (> 10 mmol/L or > 900 mg/dL) increase risk of pancreatitis, fibrates should be used.

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

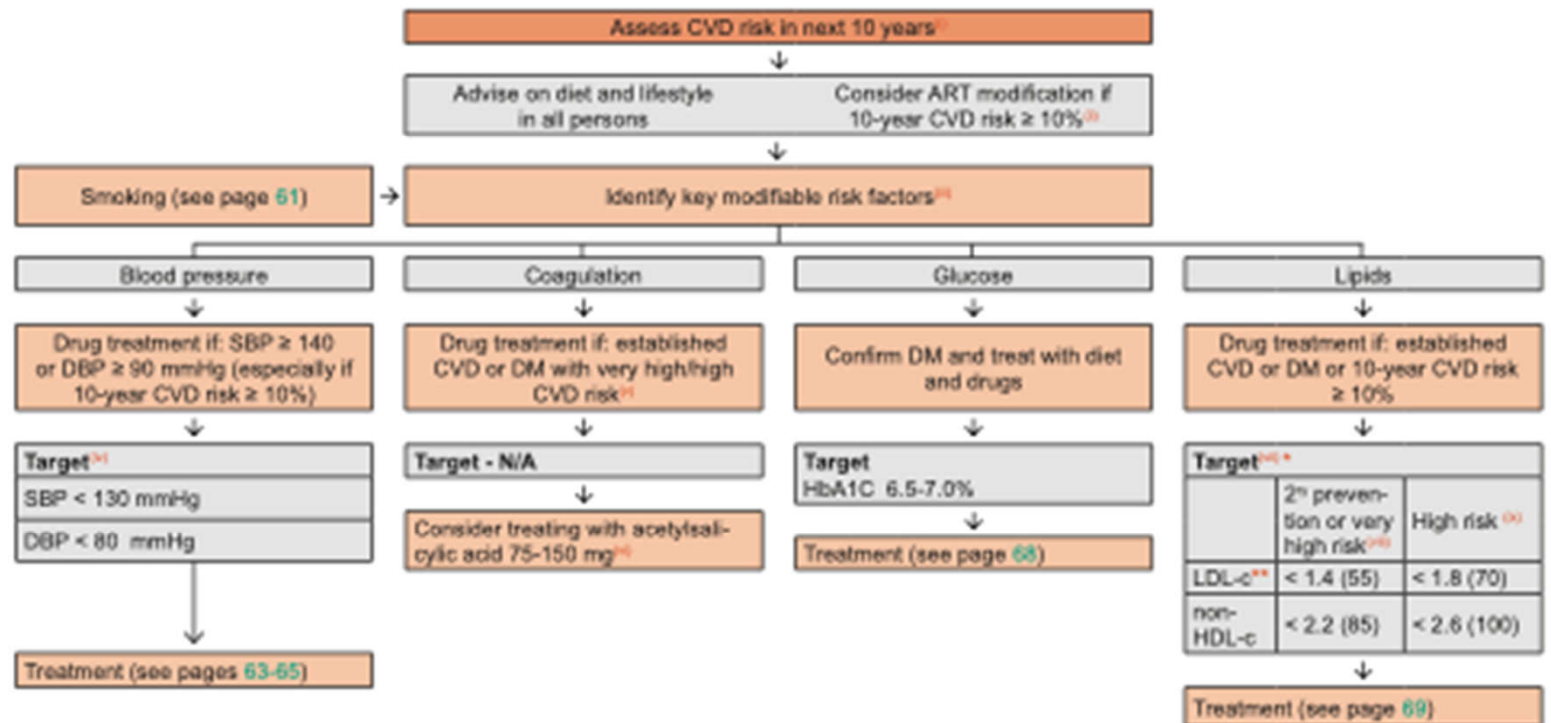


Prevention of Cardiovascular Disease (CVD)

Principles:

The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated¹. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.

- Smoking cessation
- Key lifestyle factors
 - Diet
 - Exercise
- Lipid lowering therapy, aka statins
- Aspirin
- Address other traditional factors
 - HTN
 - DM/Insulin resistance
 - Obesity
 - NAFLD/NASH



* Fasting or non-fasting samples may be used
 ** and ≥ 50% reduction from baseline

Conclusion

- Successful management of persons with HIV goes beyond provision of effective ART
- With increasing focus attributed to the appropriate management of co-morbidities in order to ensure the best outcomes.
- Persons living with HIV are twice as likely to suffer MI or stroke even after viral suppression
- Cardiovascular risk in PLWH has a unique : Traditional risk + ART+HIV
- Improving modifiable ASCVD risk factors remains by far the best way to reduce ASCVD risk in persons with HIV
 - **Smoking cessation : Important**
 - REPRIEVE data demonstrates the benefit of pitavastatin in PLWH receiving stable ART and at low –to-moderate risk ASCVD
- Multidisciplinary, holistic approach and integration of NCD package in routine HIV care