Clinical Cases Discussion

Vall d'Hebron
Barcelona Campus Hospitalari

Metabolic issues (CVR)

Adrian Curran, MD, PhD
Infectious Diseases Department
Hospital Universitari Vall d'Hebron
Barcelona

Disclosures

- I have received fees, grants and/or conference support from Gilead, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare.

- In today's session I will focus on very specific aspects, as it would be impossible to try to cover all the metabolic aspects that may have an impact on cardiovascular risk in PLWH.

David, a 51 year-old cisgender man

- **HIV** infection diagnosed in 2002, with CD4 462, VL 21.000
- Started AZT/3TC+EFV. Some detectable VL, attributed to irregular adherence. Later switched to TDF/FTC/EFV, maintaining VL<50
- Currently on **ABC/3TC/DTG** since Oct 2017, CD4 1330, VL <50 c/mL
- **Smokes** 15 cig/day, 1 beer/daily, no other drugs. “Normal” diet, little exercise
- Weight 81 kg, height 175 cm, **BMI** 26.4, **BP** 134/91
- **Current visit**:
  - No complaints, nothing new, doing OK, happy with the ART
  - Blood tests: CD4 1330, VL <50 c/mL. Glu 82, CKD 89, liver OK, col 185 (46/116), TG 114

David, a 51 year-old cisgender man

Smokes 15 cig/day, W 81 kg, H 175 cm, BMI 26.4, BP 134/91, col 185 (46/116), TG 114

https://www.thesun.co.uk/fabulous/8853261/jude-law-ordinary-men-white-pants/

What would you do with David?

- Nothing, he is doing fine, no complaints, blood tests OK. Continue with the same ART and see him in 6 months. I have 25 patients this morning, this is an easy one, let's get with the next one...
- I should evaluate David's cardiovascular risk. However, he is doing fine. I have 25 patients this morning, let's get with the next one...
- I would evaluate David's cardiovascular risk, using a score. Depending on the results I should start a statin. Insist in diet, exercise and quit smoking.
- 51, HIV... I would give him pitavastatin 4 mg/day right away. Continue with the same ART and see him in 6 months. I have 25 patients this morning, let's get with the next one...

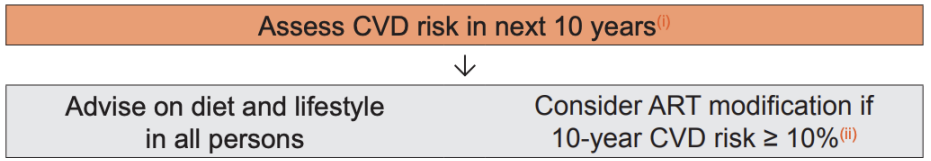
Do we have to evaluate CVR in PLWH?

Tabla 1. Exploraciones complementarias en la valoración inicial y en el seguimiento de los pacientes con infección por el VIH-1[1,2]

Actividad / Exploración	Valoración Inicial	Seguimiento
Cálculo del riesgo cardiovascular (RCV) con una escala validada	Sí	Anualmente en varones >40 años y en mujeres >50 años y cada 3-6 meses en sujetos con alto RCVP

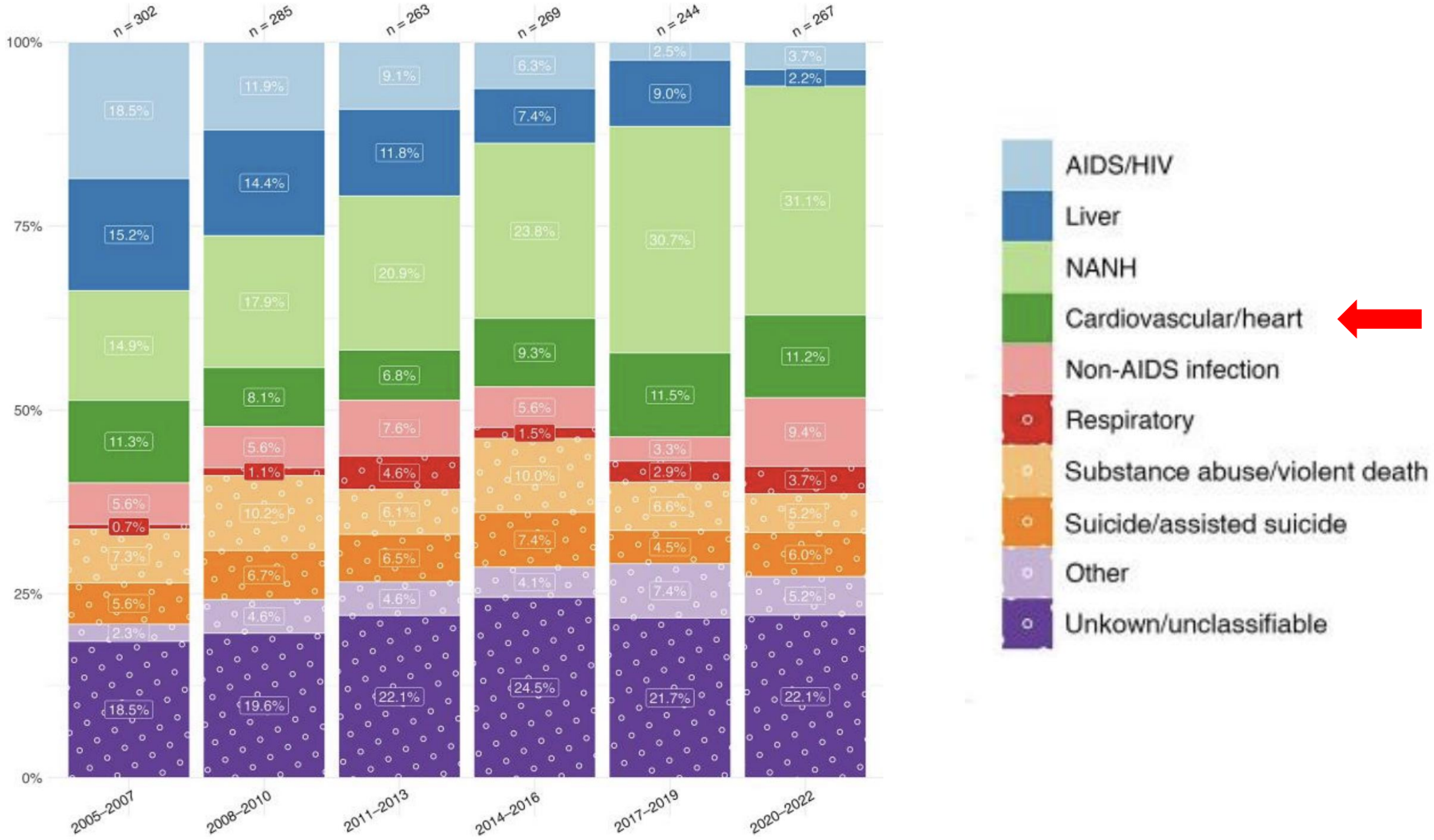
Prevention of Cardiovascular Disease (CVD)

Principles:
The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated[i]. 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.



https://gesida-seimc.org/wp-content/uploads/2023/06/Guia_TAR_V12.pdf.
https://www.eacsociety.org/media/guidelines-12.0.pdf

Causes of death in PLWH (Swiss Cohort)



Weber M et al. Clin Infect Dis 2024;79(1):177–88

CVR in PLWH

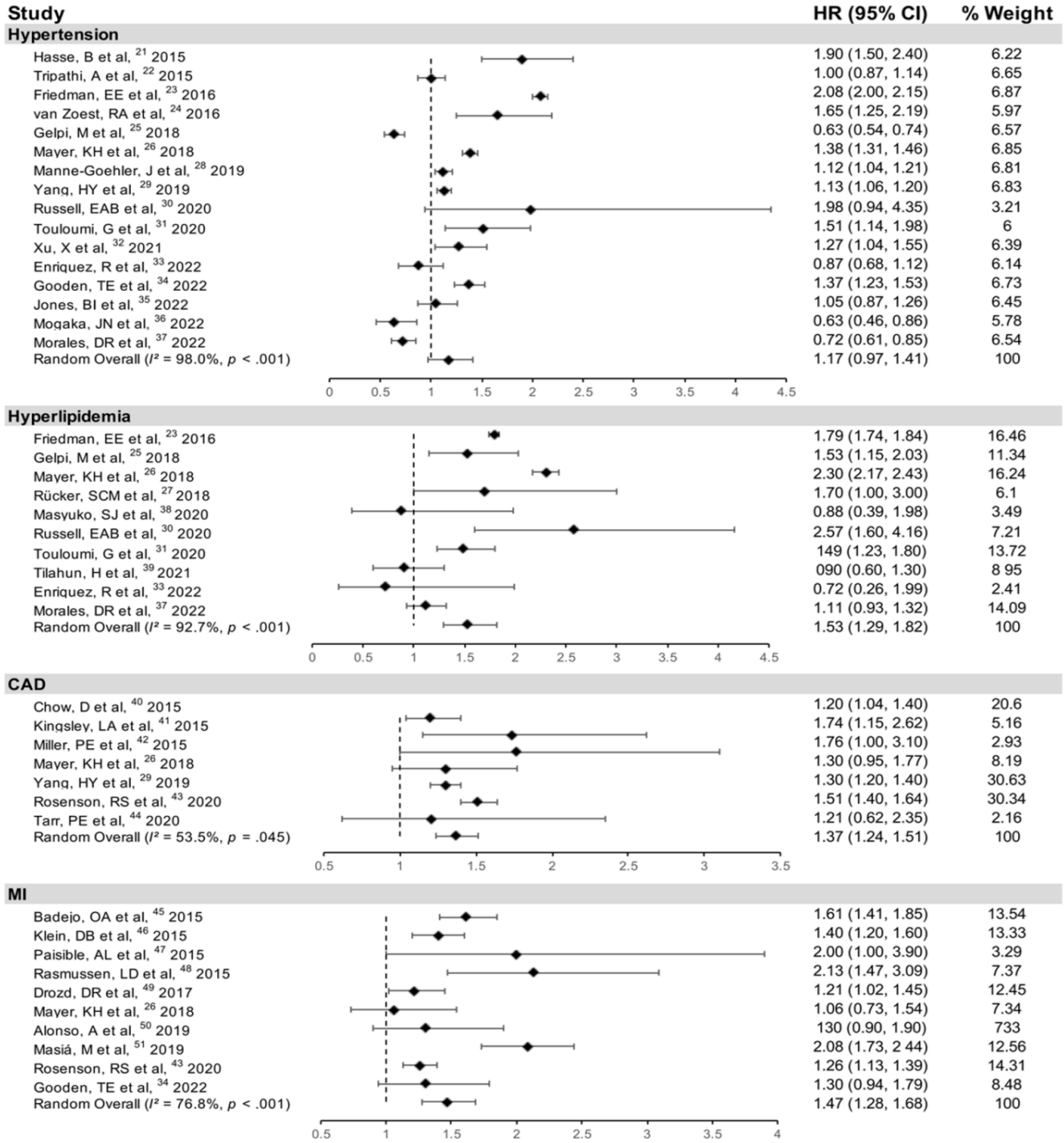
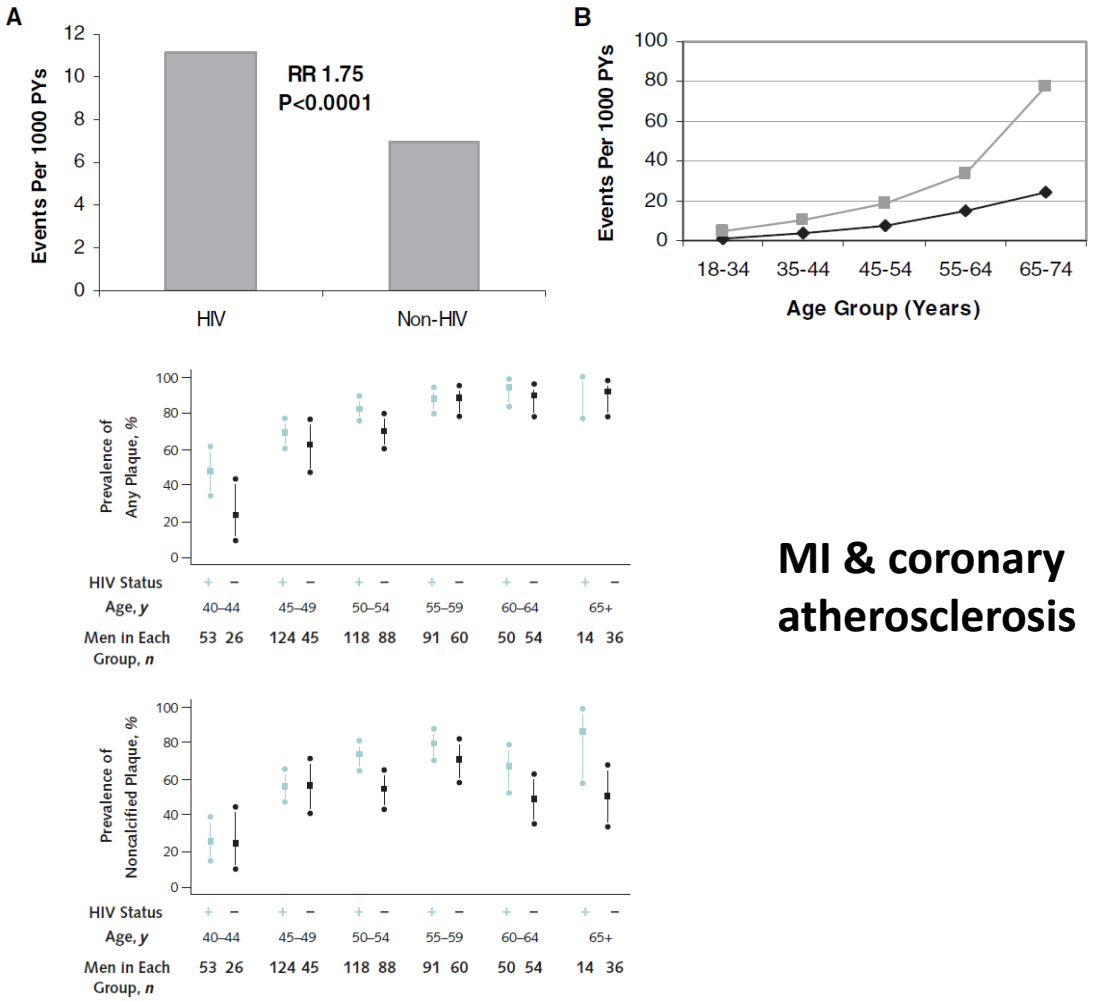


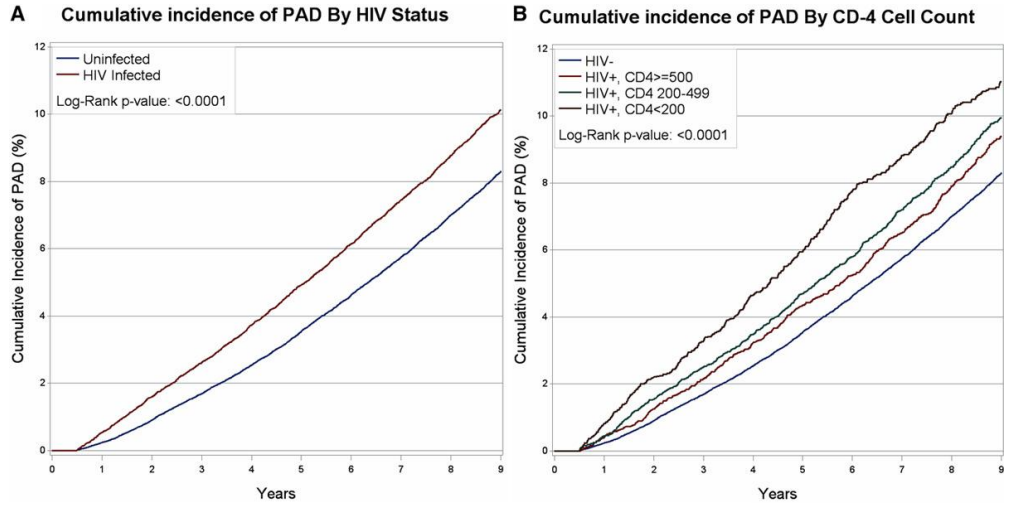
Figure 3. Pooled HRs of hypertension, dyslipidaemia, CAD, and MI in PLWH compared to the general population. CAD – coronary artery disease, CI – confidence interval, HR – hazard ratio, MI – myocardial infarction, PLWH – people living with HIV

San Z, et al. Higher cardiovascular disease risks in people living with HIV: A systematic review and meta-analysis. J Glob Health 2024;14:04078.

CVR in PLWH

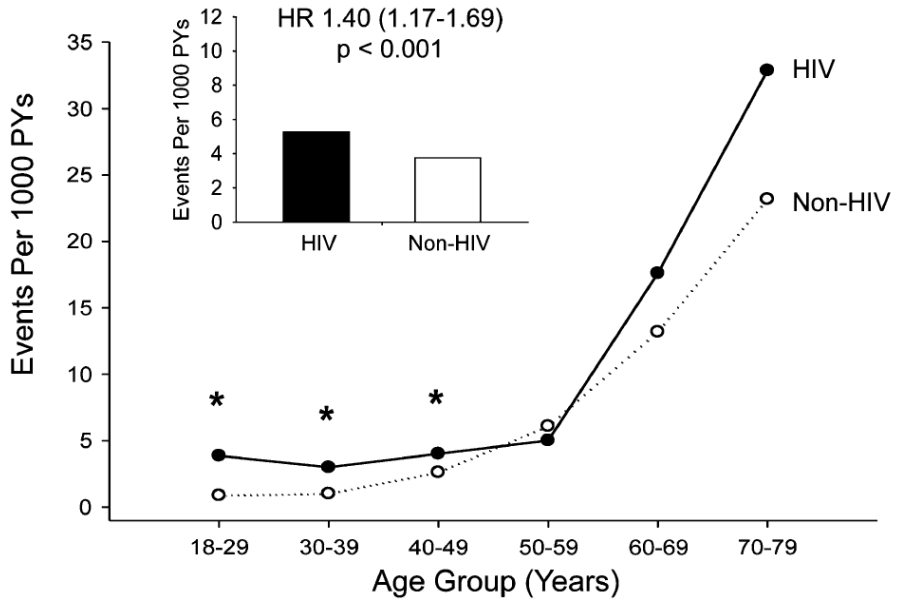


MI & coronary atherosclerosis



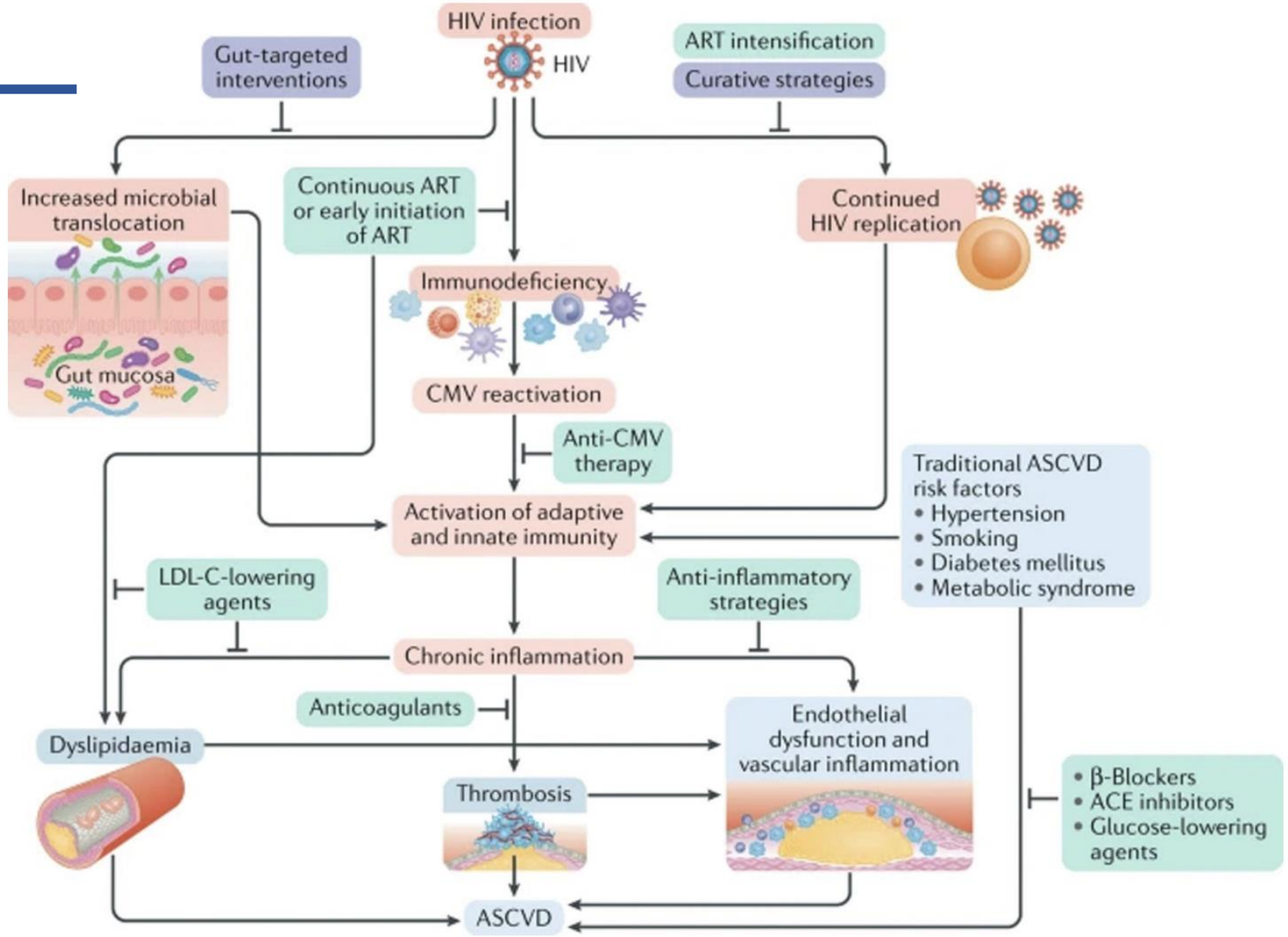
PAD

Stroke



Triant VA, et al. *J Clin Endocrinol Metab* 2007;92:2506-12 Post WS, et al. *Ann Intern Med* 2014;160:458-67. Beckman JA, et al. *Circulation* 2018;138:255–265. Chow FC, et al. *JAIDS* 2012;60:351-8

CVR in PLWH



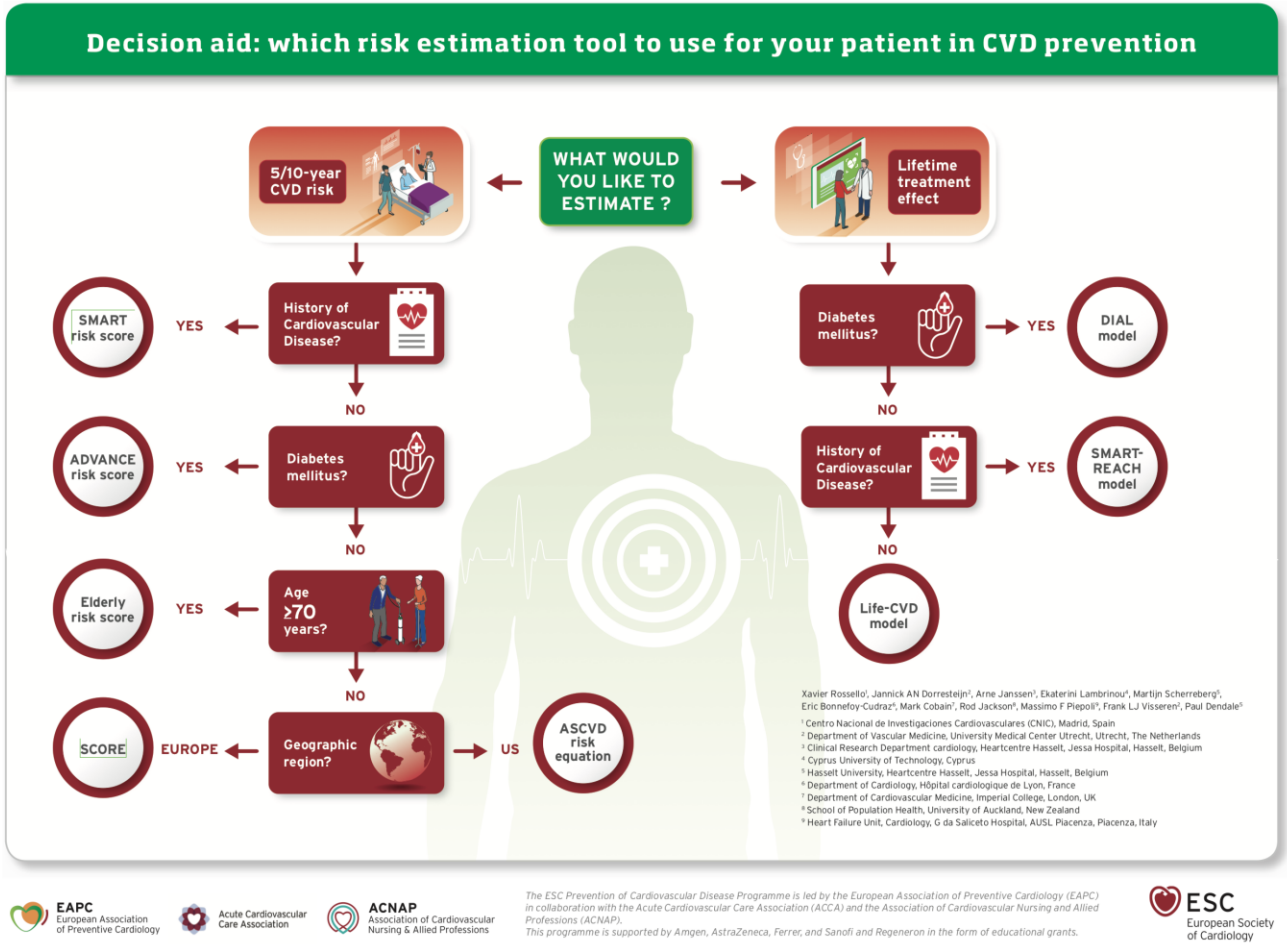
Pathophysiology and management of HIV-associated atherosclerotic cardiovascular disease.

Hsue P et al. Nat Rev Cardiol. 2019; 16(12): 745–759.

If you want to evaluate David's CVR, which tool would you use?

- Score 2 (European Society of Cardiology)
- ACC/AHA- ASCVD
- Framingham Heart Study
- Other

Clinical scores



Overview of freely accessible online tools for estimation of cardiovascular prognosis

TOOL	Patient categories	Geographical region	Prediction outcomes	Additional features
SCORE www.heartscore.org	Healthy people	Europe high and low risk regions	10-year CVD risk	Personal health advice based on ESC-Guidelines Available in 17 languages Print option for patient handout Patient history and progress Calibrated versions
QRISK3 www.qrisk.org/three	Healthy people	United Kingdom	10-year CVD risk Relative risk Heart age	Infographics for patient communication
JBS-3 risk calculator www.jbs3risk.com	Healthy people	United Kingdom	10-year CVD risk Lifetime CVD risk Heart age CVD-free life-expectancy	Effect of risk factor optimisation Infographics for patient communication
ASSIGN score www.assign-score.com	Healthy people	Scotland	10-year CVD risk	Missing data filled in by population average/median Print option for patient handout
PROCAM score Various websites	Healthy people	Germany	10-year coronary event risk	
CUORE www.cuore.iss.it/sopra/calc-rischio_en.asp	Healthy people	Italy	10-year CVD risk	Also available in Italian language
ASCVD risk-estimator plus http://tools.acc.org/ASCVD-Risk-Estimator-Plus	Healthy people	United States	10-year CVD risk Lifetime CVD risk	Effect of risk factor optimisation Personal health advice based on ACC/AHA guidelines Print option for patient handout
Framingham risk score www.framinghamheartstudy.org	Healthy people	United States	10-year CVD risk 30-year CVD risk Heart age	Additional calculators for other vascular disease outcomes
Reynolds risk score www.reynoldsriskscore.org	Healthy people	United States	10-year CVD risk Relative risk	Effect of risk factor optimisation Projection of risk increase with advancing age Print option for patient handout
Globorisk www.globorisk.org	Healthy people	Worldwide	10-year CVD risk	Country adjusted risk charts available
UKPDS risk engine V2 www.dtu.ox.ac.uk/riskengine	Type 2 diabetes	United Kingdom	Fatal and non-fatal CVD risk for any risk interval	Print option for patient handout
ADVANCE risk engine www.advanceriskengine.com	Type 2 diabetes	Europe, Asia, Australasia and North America	4-year CVD risk	Missing data filled in by population average/median Additional calculator for kidney disease outcomes
SMART risk score www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score	Vascular patients	Europe and United States	10-year CVD risk	Missing data filled in by population average/median
MAGGIC risk calculator www.heartfailurerisk.org	Heart failure patients	Worldwide	1 and 3-year mortality risk	
Seattle Heart Failure model www.SeattleHeartFailureModel.org	Heart failure patients	Northern-America	1, 2 and 5-year mortality risk	Effect of specific treatment options
U-Prevent www.U-prevent.com	Healthy people Type 2 diabetes patients Vascular patients Elderly	Europe and Northern-America	10-year CVD risk Lifetime CVD risk CVD free life expectancy	Also available in Dutch Effect of specific treatment options Effect of deferred treatment Infographics for patient communication Print option for patient handout Missing data filled in by population average/median Calculator selection aid

https://www.escardio.org/static-file/Escardio/Subspecialty/EAPC/Documents/CVDPROG%20-%20Flowchart-RiskAssessment-Other.pdf

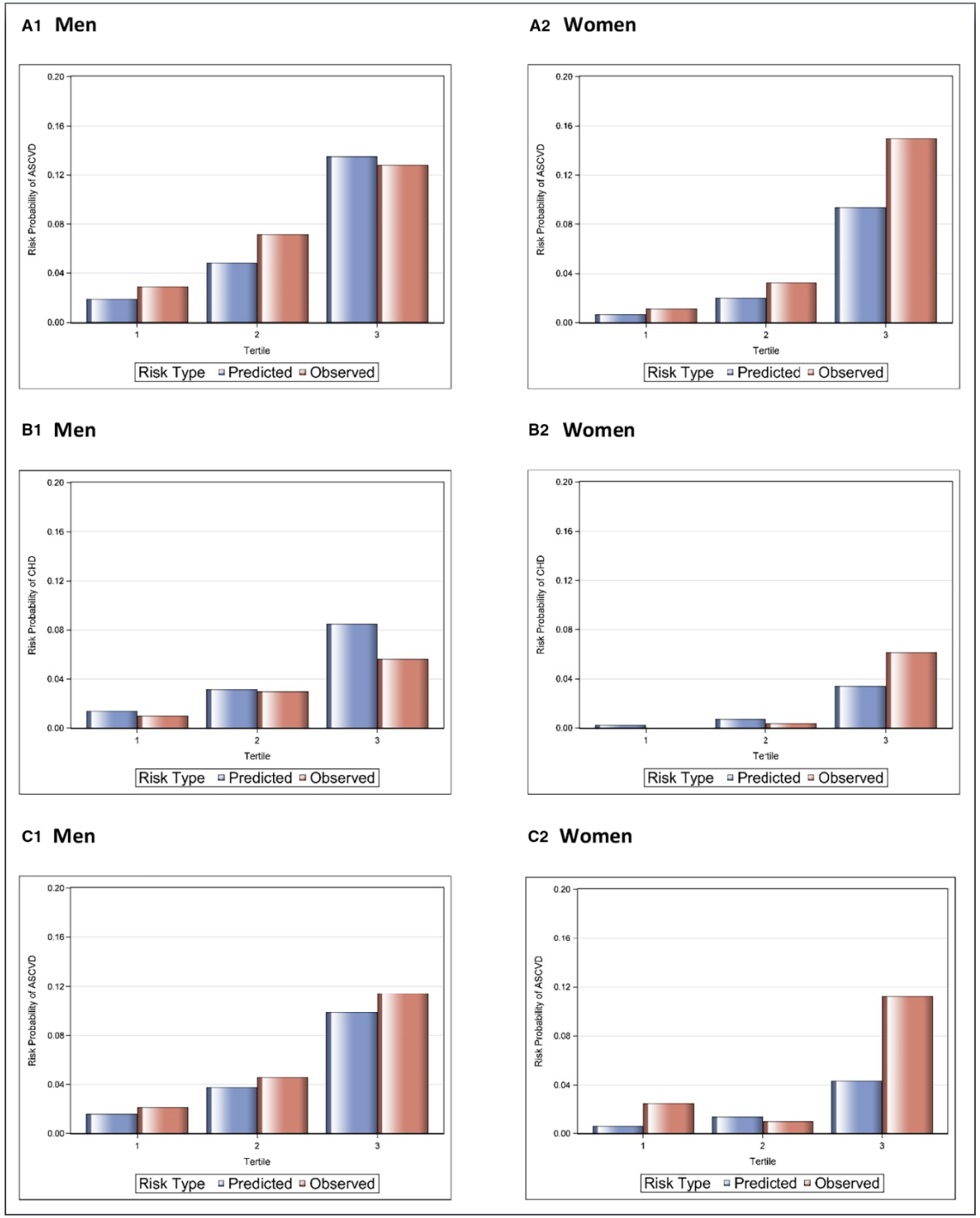
Journal of the American Heart Association
Volume 13, Issue 10, 21 May 2024
https://doi.org/10.1161/JAHA.123.029228

ORIGINAL RESEARCH

Cardiovascular Risk Estimation Is Suboptimal in People With HIV

Especially in individuals who are:

- younger
- women
- Black race
- predicted at low/ intermediate risk



ACC/AHA

FHS CHD

FHS CVD

Triant V et al. J Am Heart Assoc. 2024;13:e029228
Achra A et al. Curr HIV/AIDS Rep 2021;18: 271–279

Risk Enhancers

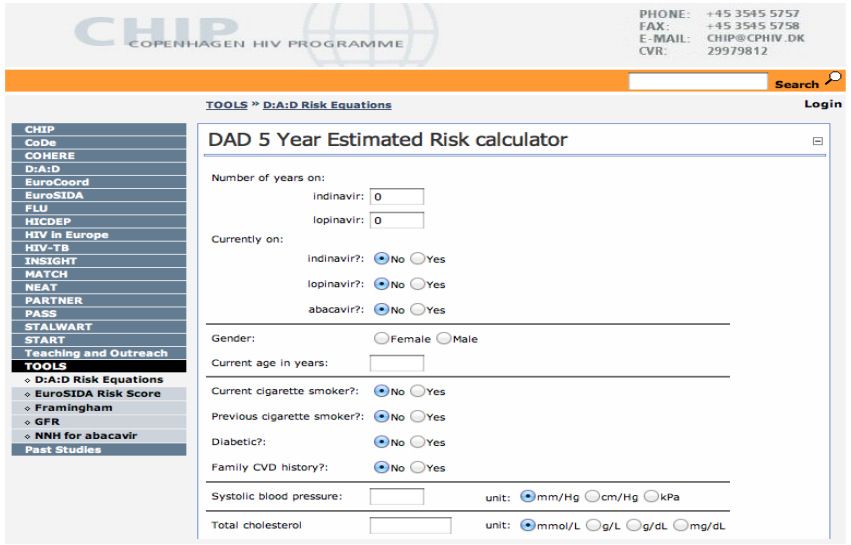
- Family history of early ASCVD (men <55 years old, women <65)
- Current high cholesterol (LDL-C 160-189mg/dl; non-HDL-C 190-219mg/dL)
- Metabolic syndrome
- Chronic kidney disease
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, psoriasis, HIV)
- History of pre-eclampsia or early menopause
- High-risk ethnicity (e.g. South Asian Ancestry)
- High lipid biomarkers
- Triglycerides ≥175 mg/dL
- High-sensitivity C-reactive protein ≥2.0mg/dL
- Elevated lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L
- Elevated apolipoprotein B ≥130 mg/dL
- Ankle-brachial index (ABI) ‹0.9

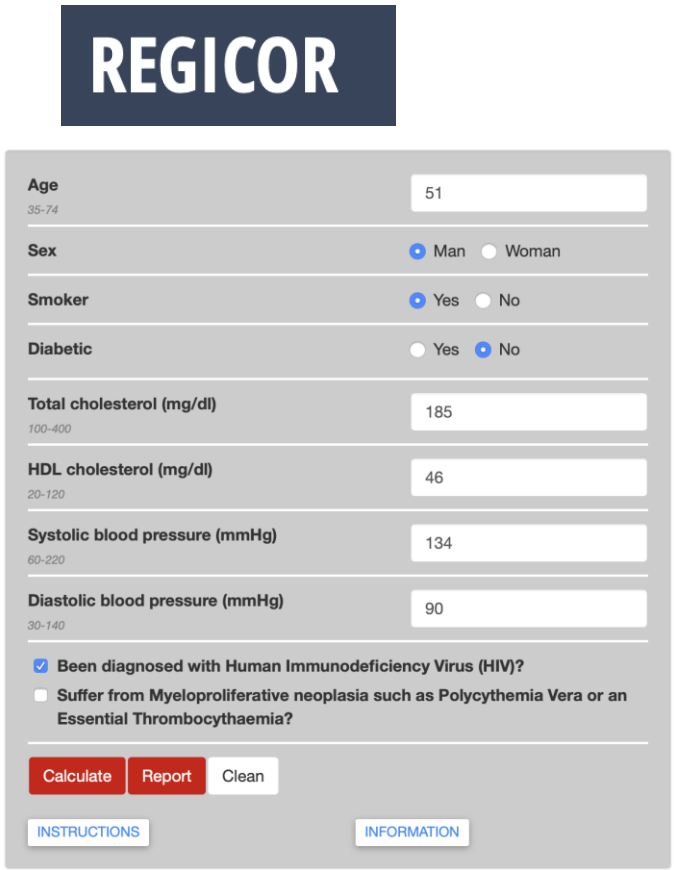
HIV-related risk enhancers
Prolonged HIV viremia/delay in cART initiation
Current or nadir CD4 <350 cells/mm^3
HIV treatment failure or nonadherence
Metabolic syndrome, lipodystrophy, fatty liver disease
HCV co-infection

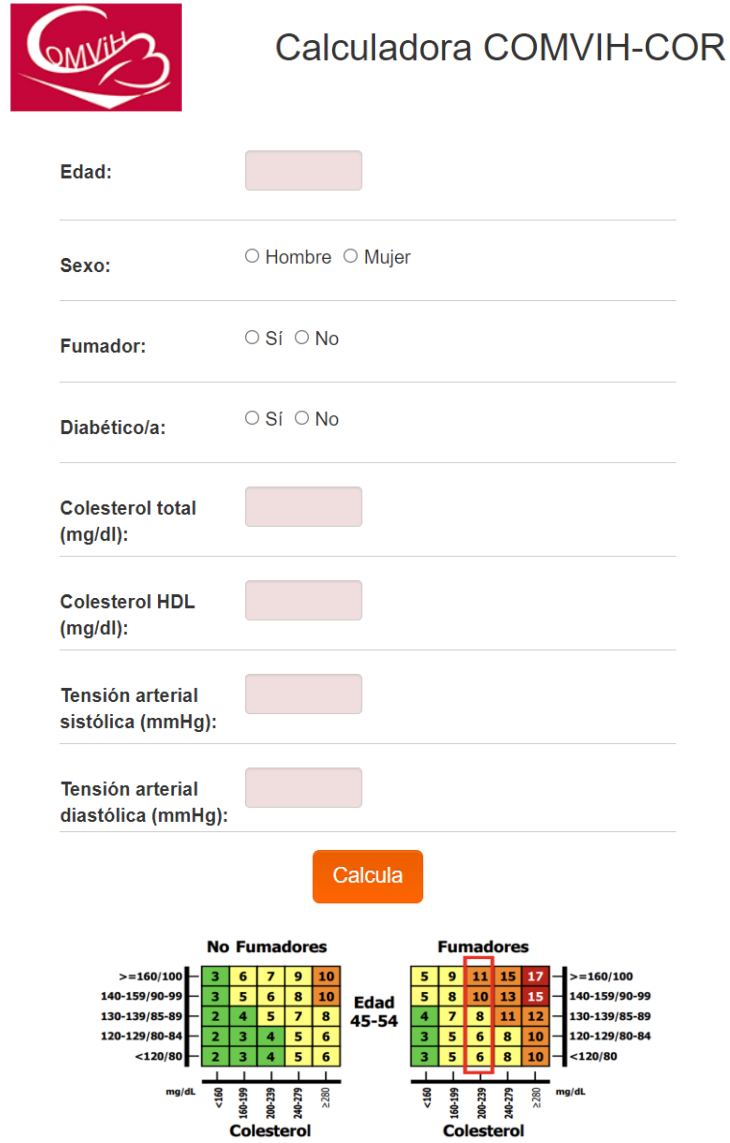
Specific ART?

https://static.heart.org/riskcalc/app/index.html#!/baseline-risk

Clinical scores HIV







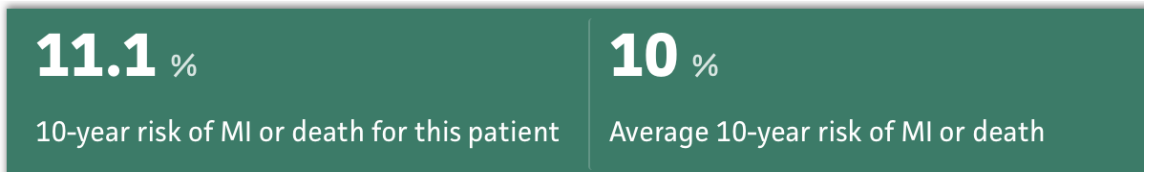
http://www.cphiv.dk/tools/dadriskequations/tabid/437/default.aspx; https://regicor.cat/aplicacions/regicor/; https://comvih-cor.datarus.eu/es/calculadora

Clinical scores

D:A:D Full model/Reduced model

ACC/AHA-ASCVD

Framingham Heart Study (FHS-CVD)



ESC SCORE2 (SCORE2-OP)

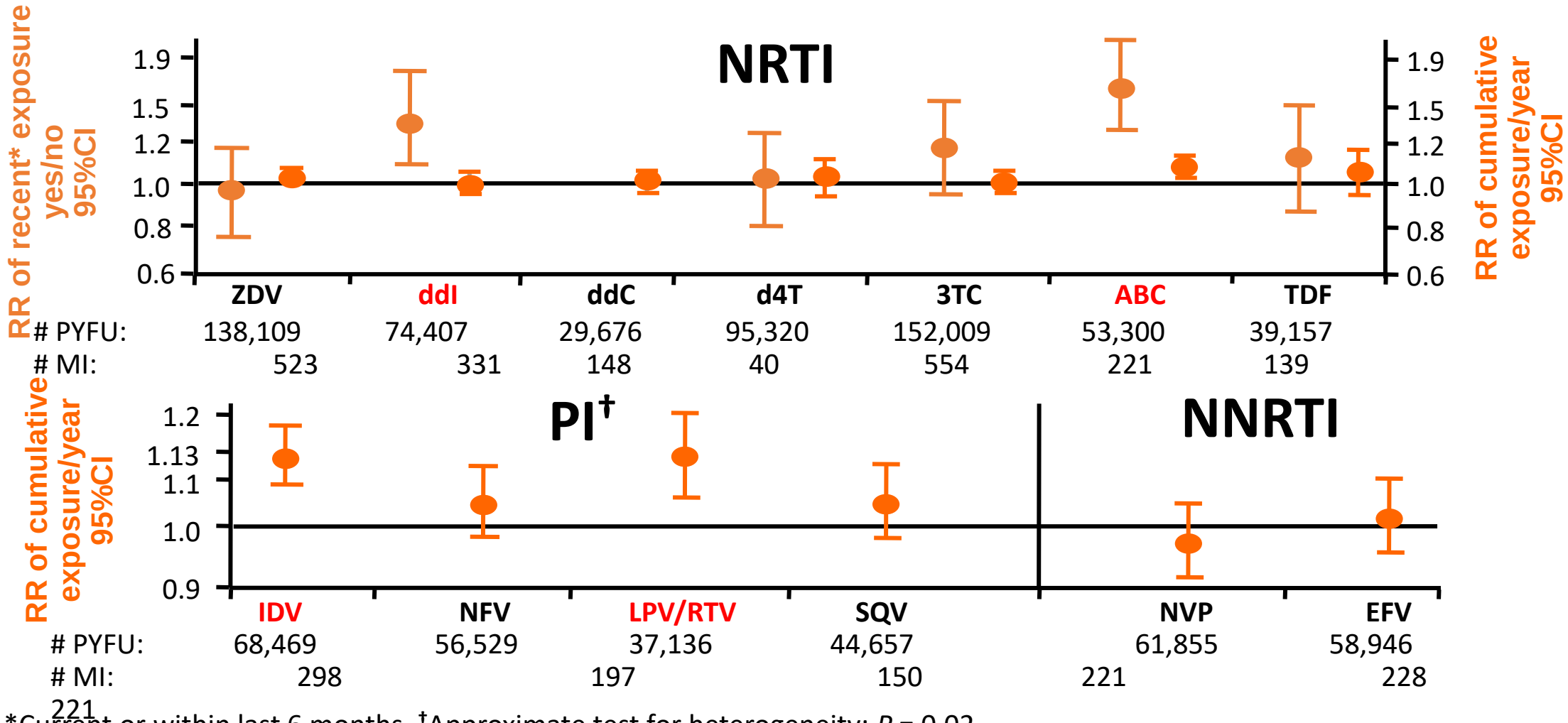
https://www.chip.dk/Resources/Clinical-risk-scores; https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ http://static.heart.org/riskcalc/app/index.html#!/baseline-risk). https://www.escardio.org/Education/ESCPrevention-of-CVDProgramme/Risk-assessment/esc-cvd-risk-calculation-app)

Do you think David's ART increases CVR?

- Abacavir
- INSTIs
- ABC and INSTIs
- NO

Would you change ART?

CVR in PLWH. Related to ART?

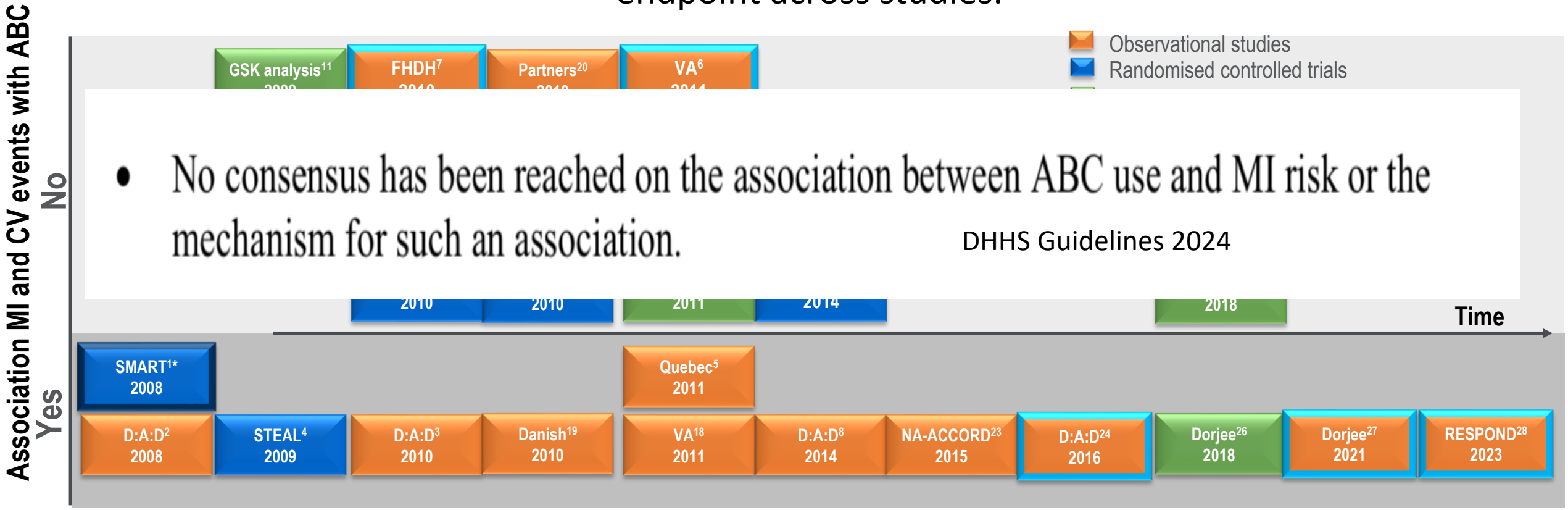


*Current or within last 6 months. †Approximate test for heterogeneity: $P = 0.02$

Worm SW et al. *JID* 2010; 201: 318-30.

CVR in PLWH. Related to Abacavir?

Studies measuring myocardial infarction (MI) or cardiovascular events: No consistent endpoint across studies.

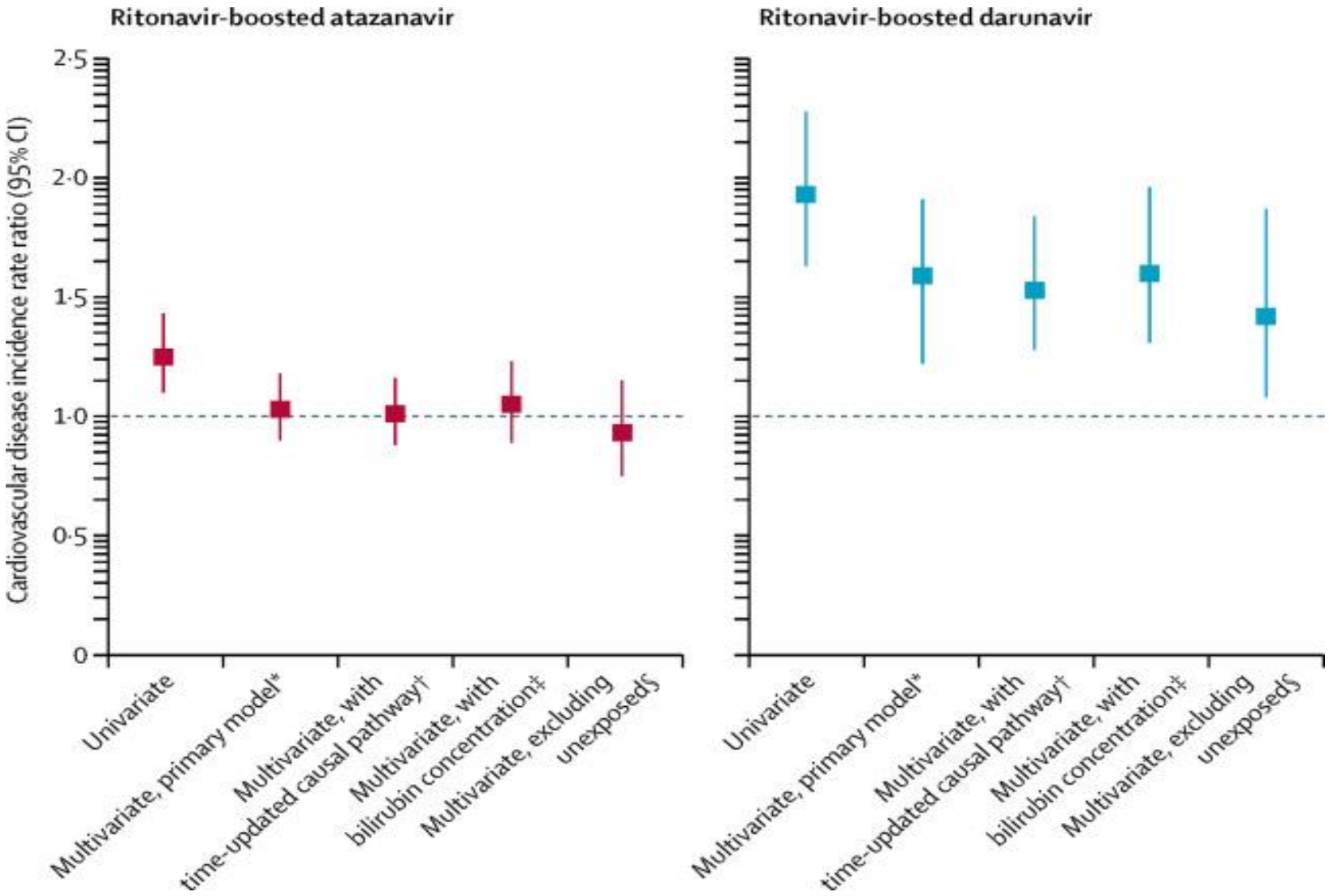


- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

DHHS Guidelines 2024

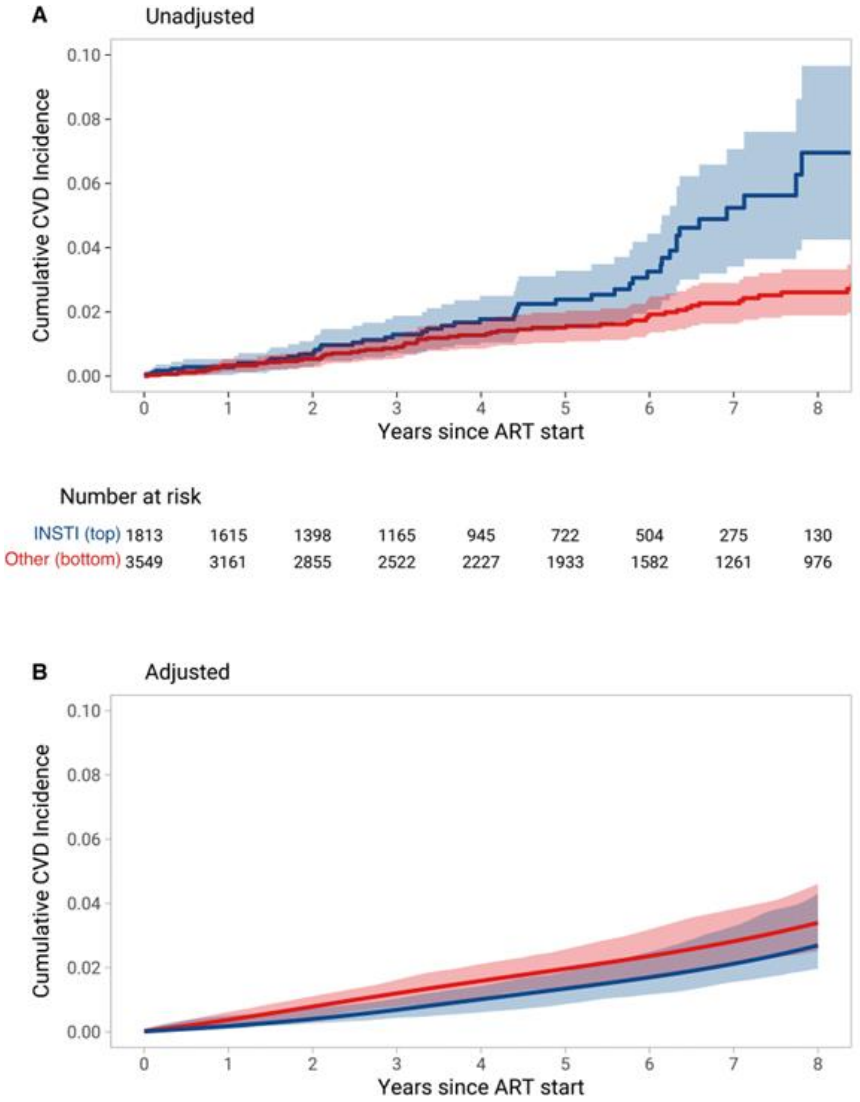
1. SMART Study Group. AIDS 2008;22:F17-F24; 2. Sabin CA et al. Lancet 2008;371:1417-26; 3. Worm SW et al. J Infect Dis 2010;201:318-30; 4. Martin A et al. CID 2009;49:1591-601; 5. Durand M et al. JAIDS 2011;57:245-53; 6. Bedimo RJ et al. Clin Infect Dis 2011;53:84-91; 7. Lang S et al. Arch Intern Med 2010;170:1228-38; 8. Sabin CA et al. 21st CROI; 2014; Abstract 747LB.; 9. Ribaudo HJ et al. Clin Infect Dis 2011;52:929-40; 10. Smith KY et al. AIDS 2009, 23:1547-56; 11. Brothers CH et al. JAIDS 2009;51;20-8; 12. Squires K et al. AIDS 2010, 24:2019-27; 13. Martinez E et al. AIDS 2010; 24:F1-F9; 14. Ding X et al. JAIDS 2012;61:441-7; 15. Moyle G et al. Antivir Ther 2013;18:905-13; 16. Sax P et al. J Infect Dis 2011;204:1191-201; 17. Cruciani M et al. AIDS 2011; 25:1993-2004; 18. Choi AI et al. AIDS 2011;25:1289-98; 19. Obel N et al. HIV Med 2010;11:130-6; 20. Triant V et al. JAIDS 2010;55:615-9; 21. Lichtenstein K et al. Clin Infect Dis 2010;51:435-47; 22. Pappa K et al. ICAAC 2014; Abstract H-647a; 23. Palella et al. CROI 2015; Seattle, WA. Slides 749LB; 24. Sabin et al BMC Medicine 2016;14:61. 25. Nan et al. OFID 2018; 26. Dorjee et al. IJAA 2018;52:541–553. 27. Dorjee et al.AIDS Res Ther 2021;18:57; 28. Jaschinski et al. AIDS 2023;37:467-475.

CVR in PLWH. Related to bPI?



Lyom R et al. *Lancet HIV* 2018;5:.e291–300

CVR in PLWH. Related to INSTI?



Surial B et al. *Clin Infec Dis* 2023;77:729–37.

Integrase strand-transfer inhibitor use and cardiovascular events in adults with HIV: An emulation of target trials in the HIV-CAUSAL and ART-CC Collaborations

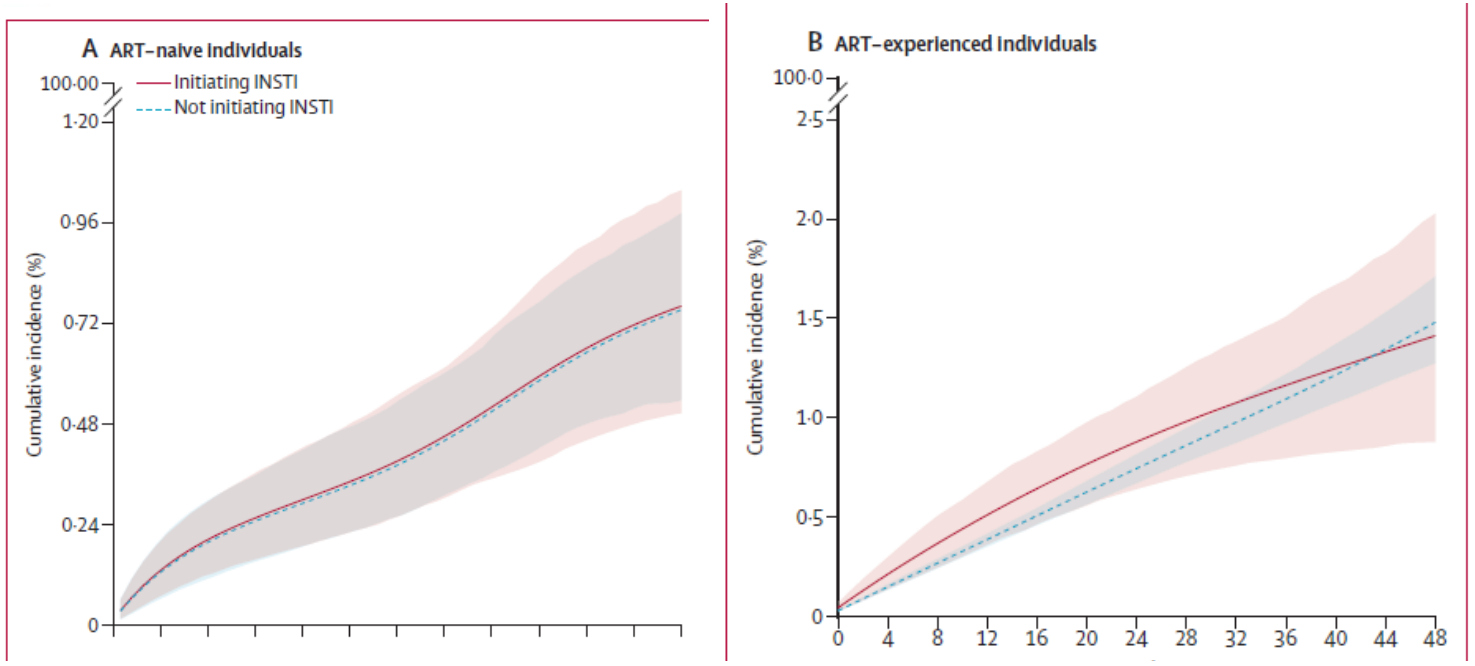


Figure 2: Estimated cumulative incidence of cardiovascular events

Rein SM et al. *Lancet HIV* 2023;10:e723–32.

Would you give statins to David?

- No, I would insist on diet and exercise, having in mind a LDL target below 130 mg/dL
- I would start with low intensity statins, to reach a LDL target of <116 mg/dL
- I would start with moderate intensity statins, to reach a LDL target of <100 mg/dL
- I would start with high intensity statins, to reach a LDL target of <70 mg/dL

CVR in PLWH. Management of lipids

Recommendations for lipid-lowering drugs in human immunodeficiency virus patients

Recommendations	Class[a]	Level[b]
Lipid-lowering therapy (mostly statins) should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high-risk patients. The choice of statin should be based on their respective potential drug–drug interactions.	IIa	C

High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).

2019 ESC/EAS Guidelines for the management of dyslipidaemias.

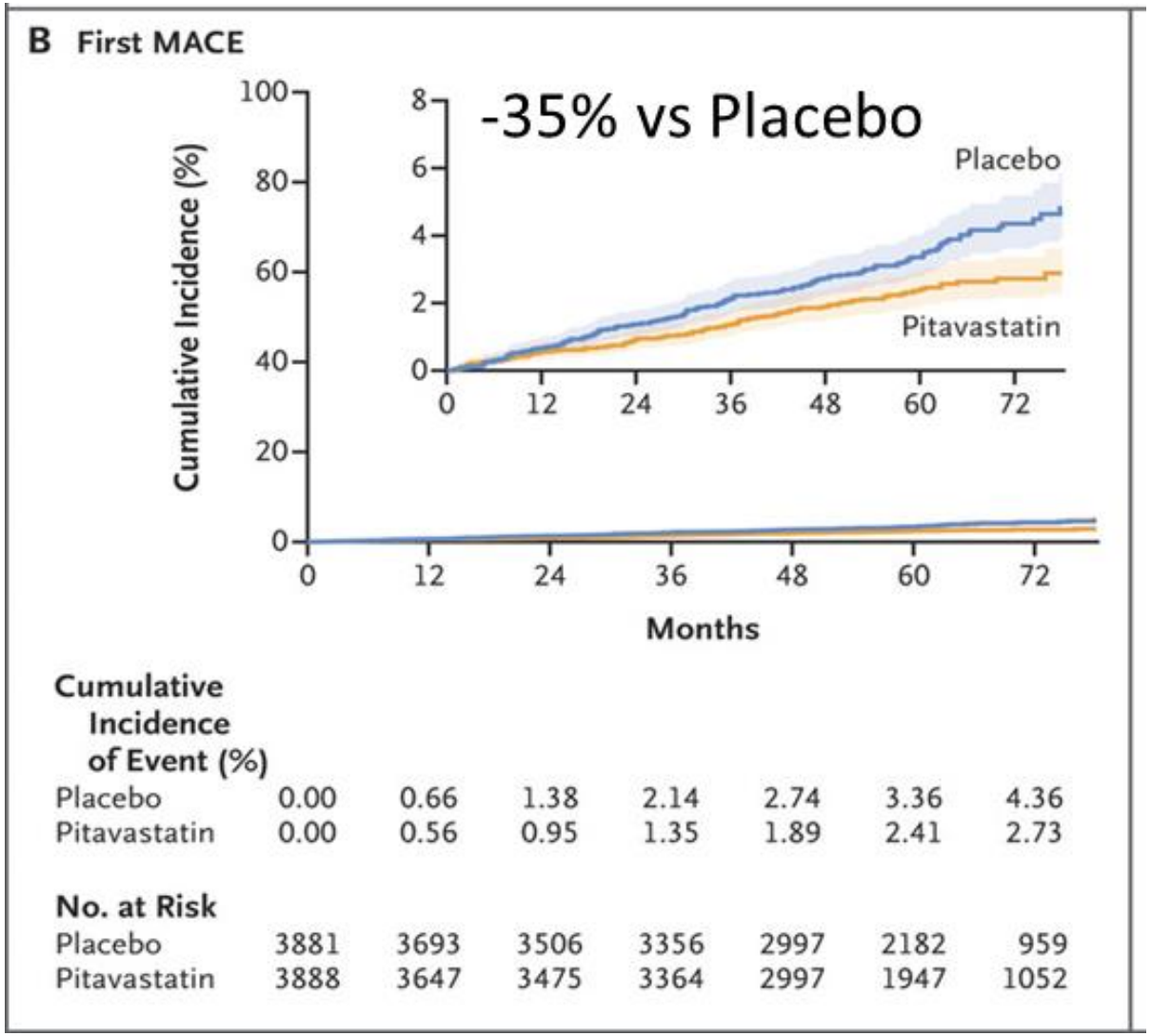
CVR in PLWH. Management of lipids

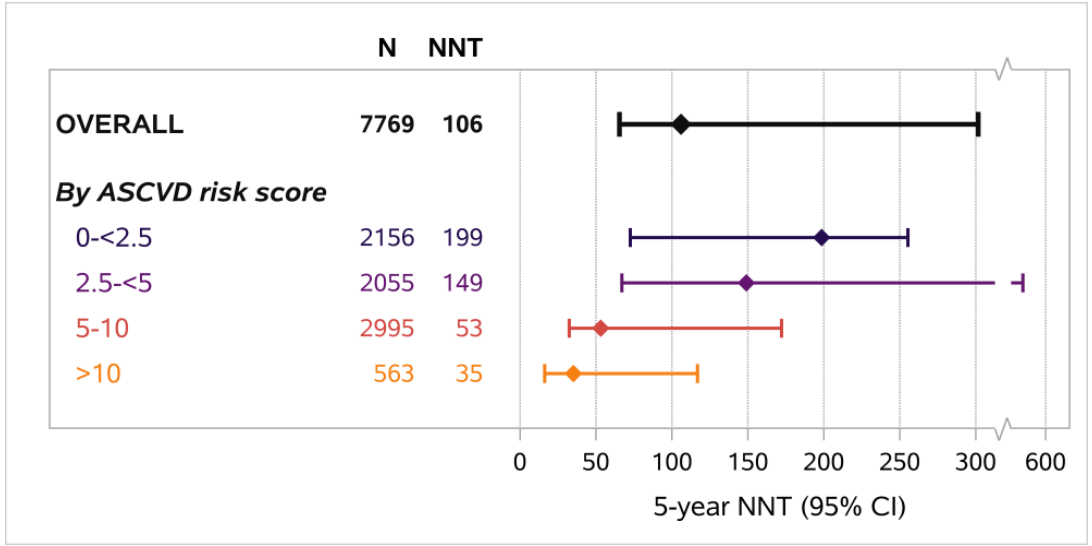
Table 5 Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

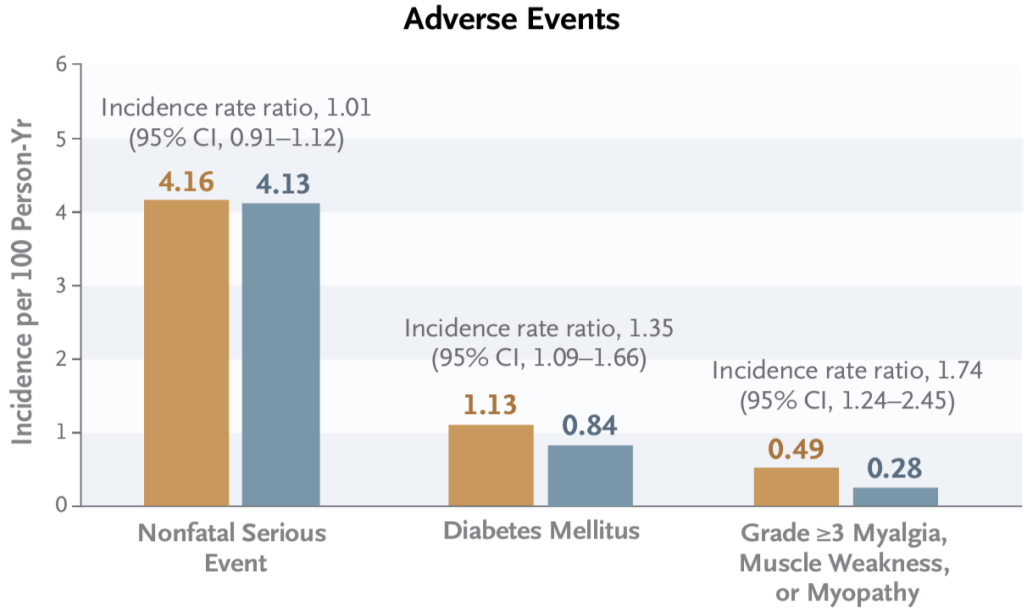
	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table* 4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table* 4)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table* 4)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

2019 ESC/EAS Guidelines for the management of dyslipidaemias.

CVR in PLWH. The REPRIEVE study







Grinspoon SK *et al. NEJM* 2023;.389:687-699

Oral Abstract Session-07

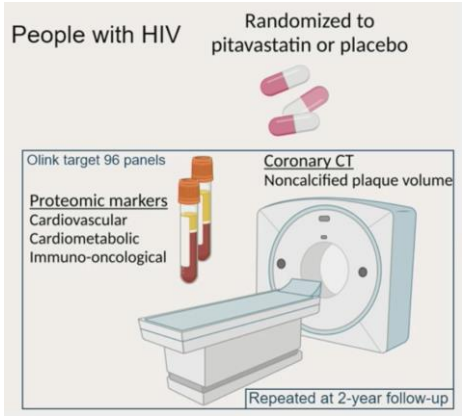
Tuesday, March 5, 2024

Pitavastatin Reduces Non-Calcified Plaque via Pro-Collagen PCOLCE Independently of LDL in REPRIEVE

Márton Kolossváry
Massachusetts General Hospital, Boston, MA, USA

Changes in LDL and biomarkers were not significantly associated with changes in noncalcified plaque volume

PCOLCE: procollagen C-endopeptidase enhancer 1
Increases procollagen maduration, adding calcium to the vascular wall (stabilyzing the plaque).



558 individuals passed all criteria for proteomic analysis
272 received Pitavastatin
286 received Placebo

Protein changes vs. noncalcified plaque change

Variable	Univariable regression			Multivariable regression		
	% change in NCP	95% Confidence interval	p	% change in NCP	95% Confidence interval	p
LDL	1.5	[-1.2; 4.3]	0.26	-0.1	[-3.0; 2.9]	0.95
ANGPTL3	-19.8	[-34.0; -2.6]	0.026	2.3	[-20.3; 31.3]	0.86
MBL2	-18.7	[-31.5; -3.5]	0.018	-11.0	[-26.9; 8.4]	0.25
MIC-A/B	-11.1	[-36.2; 23.7]	0.48	-	-	-
NRP1	-30.0	[-53.0; 4.3]	0.08	-	-	-
PCOLCE	-31.9	[-42.9; -18.7]	<0.001	-31.2	[-45.3; -13.4]	0.00

Doubling in PCOLCE expression was associated with a decrease in noncalcified plaque by -31%, [95%CI: -45%; -13%, p=0.002]

Protein changes vs. plaque components changes

Variable	Calcified plaque			Noncalcified plaque					
	Calcified plaque volume (>350HU)			Fibro-fatty plaque volume (<130HU)			Fibrous plaque volume (130-350HU)		
	% change	95% Confidence interval	p	% change	95% Confidence interval	p	% change	95% Confidence interval	p
LDL	-3.7	[-9.5; 2.3]	0.22	6.1	[0.5; 11.8]	0.032	0.4	[-1.9; 2.6]	0.74
ANGPTL3	-1.2	[-33.8; 47.5]	0.95	-28.0	[-52.3; 8.9]	0.12	-20.7	[-32.3; -7.0]	0.004
MBL2	7.3	[-25.1; 53.6]	0.70	-25.9	[-48.5; 6.8]	0.11	-13.5	[-25.0; -0.4]	0.044
MIC-A/B	6.7	[-46.4; 112.3]	0.85	-25.7	[-63.0; 49.4]	0.40	-3.3	[-26.4; 27.1]	0.81
NRP1	13.8	[-50.1; 159.5]	0.76	-46.6	[-77.0; 24.1]	0.14	-13.9	[-38.1; 19.8]	0.37
PCOLCE	34.4	[-7.9; 96.2]	0.12	-38.5	[-58.1; -9.7]	0.013	-22.2	[-32.9; -9.7]	0.001
TFPI	77.3	[-0.4; 215.4]	0.051	-0.6	[-43.8; 75.8]	0.98	-8.1	[-26.4; 14.9]	0.46
TRAIL	9.6	[-40.2; 100.7]	0.77	16.2	[-37.7; 124.1]	0.61	-9.9	[-29.8; 15.6]	0.41

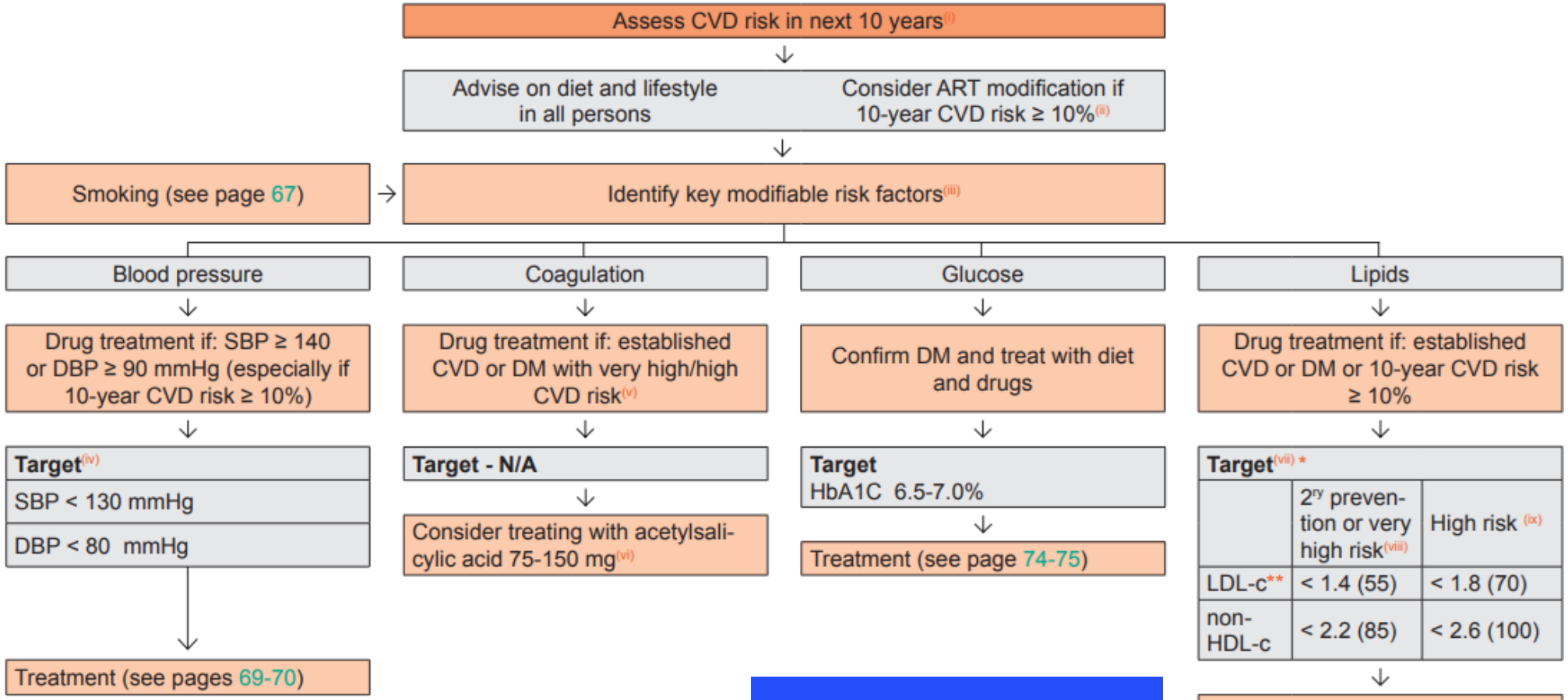
Increased PCOLCE expression was associated with a shift in plaque components promoting plaque stabilization

84% of the total effect of statins on NCP volume change was mediated through PCOLCE, independent of LDL change or achieved LDL

Kolossvary M et al. Abstract 151. CROI 2024. Denver


REPRIEVE

CVR in PLWH. Management of lipids



https://www.eacsociety.org/media/guidelines-12.0.pdf

Statin Therapy in People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV

Statement released: February 27, 2024

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new

HIV-related risk enhancers

Prolonged HIV viremia/delay in cART initiation
Current or nadir CD4 <350 cells/mm^3
HIV treatment failure or nonadherence
Metabolic syndrome, lipodystrophy, fatty liver disease
HCV co-infection

Specific ART?

Panel's Recommendations

For People With HIV Who Have Low-to-Intermediate (<20%) 10-Year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimates

- Age 40–75 Years
  - When 10-year ASCVD risk estimates are 5% to <20%, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) recommends initiating at least moderate-intensity statin therapy **(AI).**
    - Recommended options for moderate-intensity statin therapy include the following:
      - Pitavastatin 4 mg once daily **(AI)**
      - Atorvastatin 20 mg once daily **(AII)**
      - Rosuvastatin 10 mg once daily **(AII)**
  - When 10-year ASCVD risk estimates are <5%, the Panel favors initiating at least moderate-intensity statin therapy **(CI).** The absolute benefit from statin therapy is modest in this population; therefore, the decision to initiate a statin should take into account the presence or absence of HIV-related factors that can increase ASCVD risk.[a]
    - Same options for moderate-intensity statin therapy as recommended for 10-year ASCVD risk estimates of 5% to <20% (see above)
- Age <40 Years
  - Data are insufficient to recommend for or against statin therapy as primary prevention of ASCVD in people with HIV. In the general population, lifestyle modifications are recommended for people age <40 years, with statin therapy considered only in select populations (see American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines).

BHIVA rapid guidance on the use of statins for primary prevention of cardiovascular disease in people living with HIV v2

22 March 2024
Review date: 22 March 2025

Version control:

- V1 original rapid guidance
- V2 updated in light of comments received via the BHIVA website:
  - Adherence paragraph moved from communication section and combined with paragraph in adherence section.
  - Other changes highlighted.

Laura Waters, Yvonne Gilleece, Jasmini Alagaratnam, Ben Cromarty, Ming Lee, Nadia Naous, Nicoletta Policek, Caroline Sabin, John Walsh, Alan Winston, Kausik K Ray

Introduction

In cohort studies, compared to the general population or controls without HIV, people living with HIV are at greater risk of atherosclerotic cardiovascular disease (CVD) [1]. There are established national guidelines for the primary prevention of CVD with statins [2]. Because general population CVD risk calculators may underestimate risk in people living with HIV [3], HIV is considered an additional CVD risk factor in the National Institute for Health and Care Excellence (NICE) guidelines [2], but there are no specific recommendations for people living with HIV. REPRIEVE, the largest randomised trial undertaken in people living with HIV, demonstrated a significant reduction in major adverse cardiovascular events (MACE) in participants randomly assigned to pitavastatin 4 mg daily as compared to those receiving placebo [4]. Here we provide rapid guidance on the implications of the REPRIEVE study for clinical practice. Statins are an effective tool to reduce CVD risk but should be considered in the context of holistic lifestyle optimisation with a particular focus on smoking cessation. While current guidelines in primary prevention focus on estimated 10-year CVD risk, the goal of this guidance is to attenuate lifetime not just 10-year risk.

Strategy

The scope, purpose and guideline topics were agreed by the writing group, and the question was defined as 'Is there specific evidence for CVD prevention strategies (e.g. statins) for people living with HIV'. A systematic literature search of Medline, Embase and Cochrane Library databases from January 1995 to August 2023 and conference abstracts from January 2021 to August 2023 was performed. Details of the search question and strategy (including the definitions of populations, interventions, comparisons and outcomes) are available on request. For this rapid guidance, authors included publications of major importance at their discretion.

Recommendations

- We suggest that CVD risk assessment and discussion about pharmacological primary prevention is combined with a holistic approach to lifestyle modifications including smoking cessation and dietary advice, and people requiring further support should be signposted to or referred for appropriate multidisciplinary support (GPP).
- We recommend that CVD risk is assessed using tools recommended by BHIVA monitoring and national guidelines (GPP).
- We do not recommend imaging as part of CVD risk assessment for primary prevention (GPP).
- We advise baseline lipid assessment for all people living with HIV (GPP).
- We recommend excluding familial hypercholesterolaemia in all people with total cholesterol greater than 7.5 mmol/L without clear cause or a personal/immediate family history of coronary artery disease below the age of 60 years (Grade 1C).
- We recommend optimising antiretroviral therapy in people at high risk of CVD in line with BHIVA treatment guidelines (Grade 1C).
- We recommend that all people living with HIV aged 40 years or older should be offered a statin for primary prevention of CVD irrespective of lipid profile or estimated CVD risk (Grade 1B).
- We suggest that people living with HIV aged 40 years or older with an estimated 10-year CVD risk of 5% or greater are prioritised for primary prevention with a statin (GPP).
- We recommend pitavastatin 4 mg daily as the first-line choice for primary prevention when it becomes available in the UK (Grade 2A).
- We suggest that atorvastatin 20 mg daily can be used as an alternative statin (Grade 2B).
- We suggest that people on a low-intensity statin should switch to one of moderate intensity if clinically appropriate and tolerated (GPP).
- For people unable to tolerate a statin, we advise offering an alternative lipid-lowering agent in line with national guidelines (GPP).
- It is best practice for statins for primary prevention to be prescribed and monitored in primary care (GPP).

https://www.bhiva.org/file/655cdf1d7dcb1/BHIVA-rapid-guidance-on-the-use-of-statins.pdf

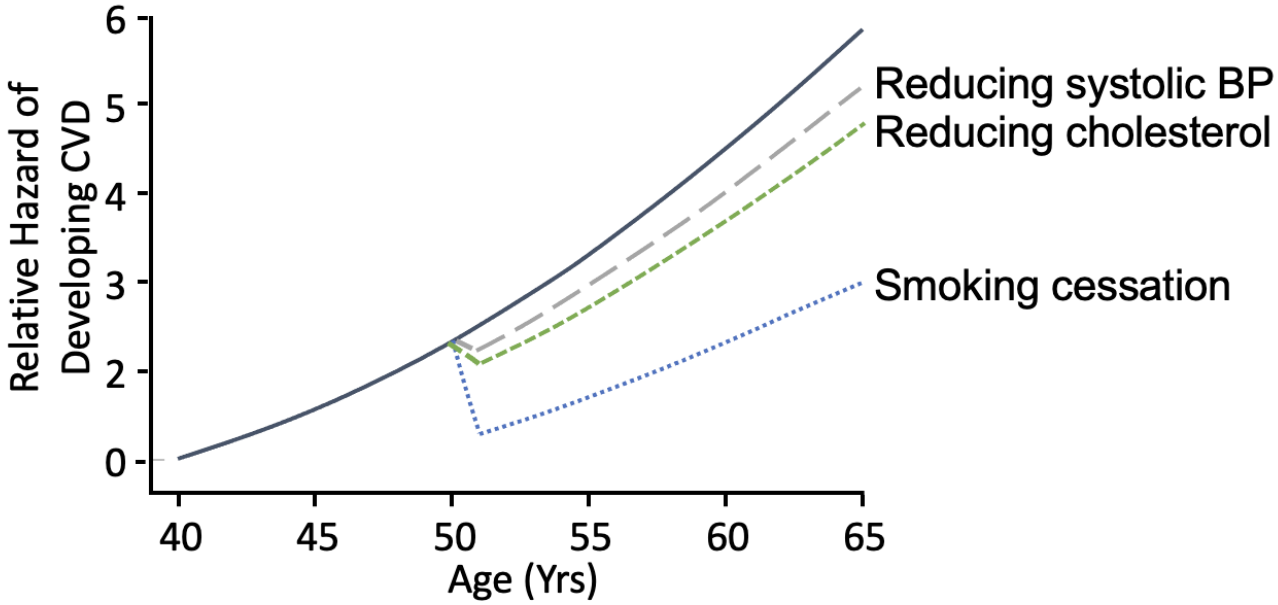
Drug-drug interactions ART-Statins

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV oral	FTR	MVC	BIC/ F/TAF	CAB oral	CAB/ RPV	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	FTC/ TAF	FTC/ TDF	TDF
Statins																						
Atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↑4%	↑	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Lovastatin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Pitavastatin	↑	↑a	↑	↓26%	↓20%	↔	↓11%	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Pravastatin	↑	↑	↑	↑81%	↔	↔	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑108%	↔	↔	↔	↔	↔	↑69%	↔	↔	↔	↔	↔	↑38%	↑38%	↔	↔	↔	↔
Simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↑	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔
Fibrates																						
Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Gemfibrozil	↔	↓	↔	↓	↓41%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Other																						
Alirocumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Evolocumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ezetimibe	↑	↑	↑	↓↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

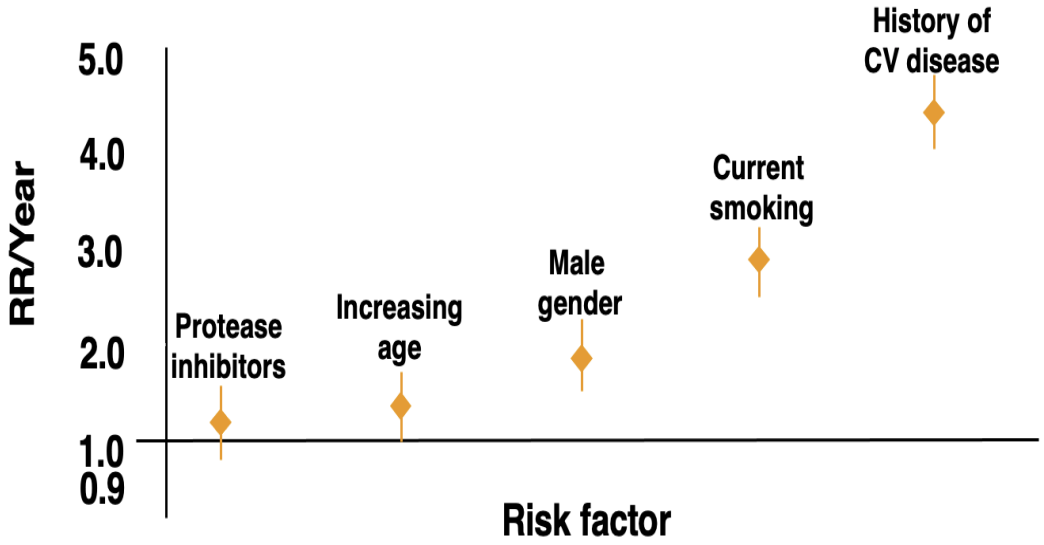
Consider: Interactions, Potency, Cost.

http://www.hiv-druginteractions.org/

Changes in lifestyle. Stop smoking

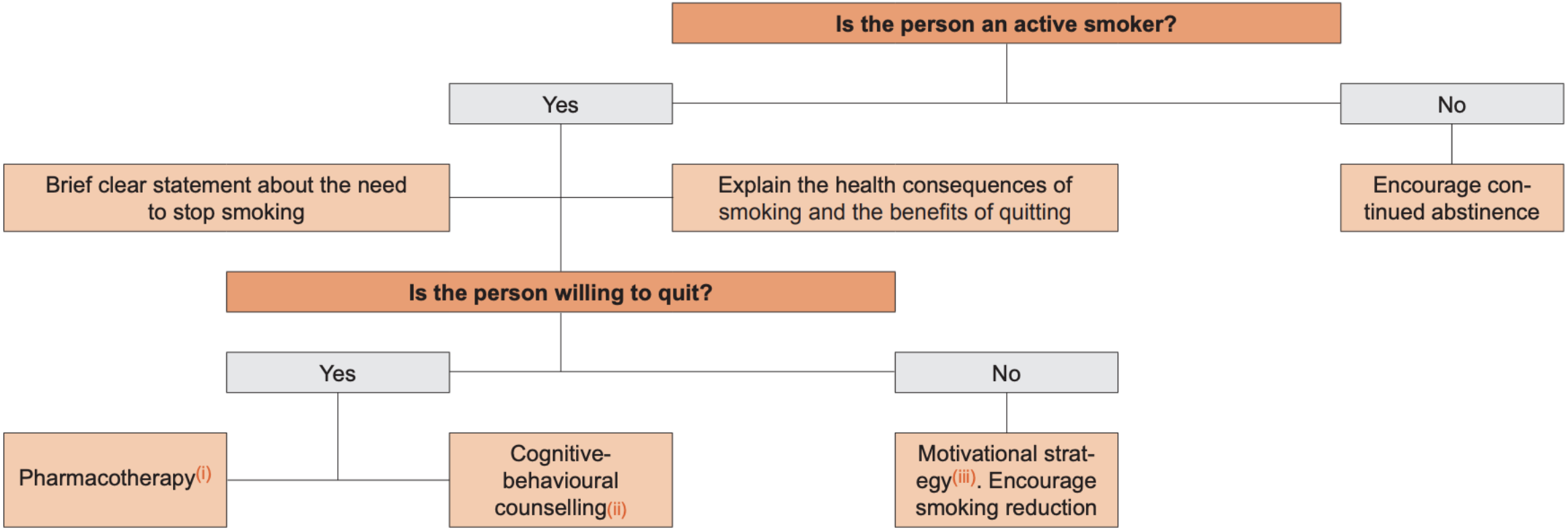


Petoumenos K, et al. *HIV Med* 2014;15:595-603.



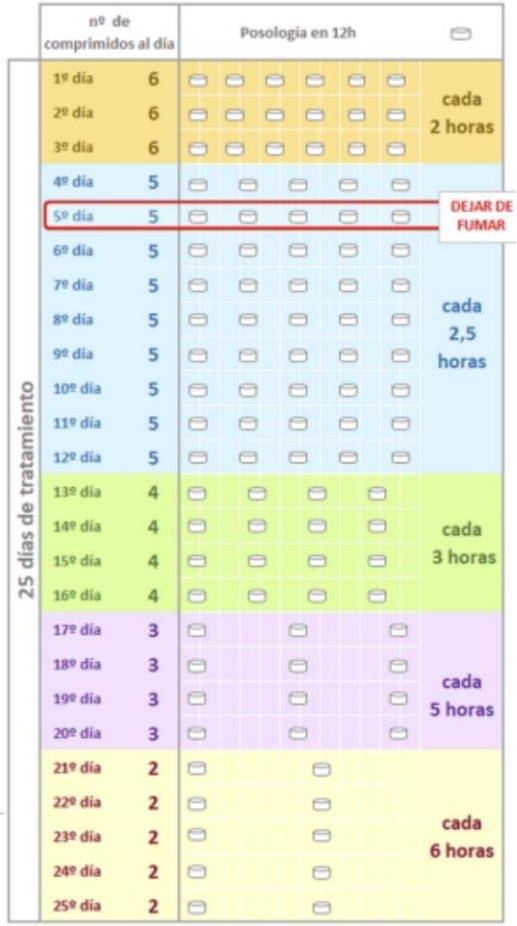
Stein JH. *N Engl J Med* 2007;356:1773–1775.

Changes in lifestyle. Stop smoking



https://www.eacsociety.org/media/guidelines-12.0.pdf

	Citisina	Bupropión		Vareniclina		
Presentación	Todacitan 1,5 mg, 100 comprimidos	Zyntabac 150 mg, 30 comp lib. prolongada	Zyntabac 150 mg, 60 comp lib. prolongada	Champix 0,5 mg y 1 mg 53 comp (Pack INICIO semanas 1-4)	Champix 0,5 mg 56 comprimidos	Champix 1 mg 56 comprimidos
Fecha financiación	01/02/2023	01/01/2020		Baja por no comercialización (01/01/23)		
Indicación financiada	**Se financiará un solo tratamiento farmacológico de deshabituación tabáquica al año**					
Duración del tratamiento financiada	Duración: 25 días	Tratamiento máximo de 7-9 semanas		Tratamiento máximo de 12 semanas		
Posología (ficha técnica)	**días 1-3:** 6 comp/día **días 4-12:** 5 comp/día **días 13-16:** 4 comp/día **días 17-20:** 3 comp/día **días 21-25:** 1-2 comp/día	**días 1-6:** 150 mg/día (1 comp/ día) **días 7-fin:** 300 mg/día (2 comp/día) *durante 7-9 semanas (49-63 días)*		**días 1 a 3:** 0,5 mg/día **días 4-7:** 1 mg/día **día 8 -84:** 2 mg/día *durante 1 sem de inicio + 11 semanas*		
Coste tratamiento año PVP	116,93 €	54,49 €		279,14 €		
Aportación paciente	Normal	Reducida		Normal		
TSI 001-0%	0	0		0,00 €		
TSI 002-10%	11,69 €	5,45 €		27,91 €		
TSI 003-40%	46,77 €	5,45 €		111,66 €		
TSI 004-50%	58,47 €	5,45 €		139,57 €		
TSI 005-60%	70,16 €	5,45 €		167,48 €		



No clinically significant interaction expected (GREEN)

Dolutegravir (DTG) + Bupropion (Amfebutamone)

Dolutegravir (DTG) + Varenicline

Darunavir/cobicistat (DRV/c) + Bupropion (Amfebutamone)

Darunavir/cobicistat (DRV/c) + Varenicline

Darunavir/cobicistat (DRV/c) + Cytisine (Cytisinicline)

Dolutegravir (DTG) + Cytisine (Cytisinicline)

https://www.hiv-druginteractions.org/

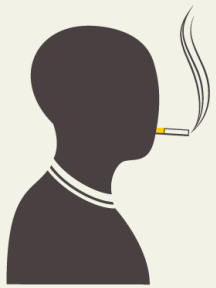
https://www.saludcastillayleon.es/portalmedicamento/es/noticias-destacados/destacados/citisina-todacitan-tratamiento-dependencia-tabaco

JAMA Network™

QUESTION Is cytisine noninferior to varenicline regarding smoking cessation?

CONCLUSION The clinical trial findings failed to demonstrate noninferiority of cytisine compared with varenicline regarding smoking cessation in adult daily smokers.

POPULATION



742 Women
710 Men

Adult daily smokers willing to make a quit attempt

Mean age: **43** years

LOCATIONS

Australia

INTERVENTION

1452 Patients randomized
1108 Patients completed final follow-up

725

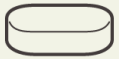
Cytisine

1.5-mg capsules taken 6 times daily initially, then reduced over 25-day course

727

Varenicline

0.5-mg tablets titrated to 1 mg twice daily for 12 weeks



PRIMARY OUTCOME

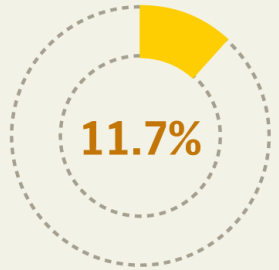
6-month continuous abstinence verified using carbon monoxide breath test at 7-month follow-up, and noninferiority set at 5%

FINDINGS

6-month biochemically verified continuous abstinence rate

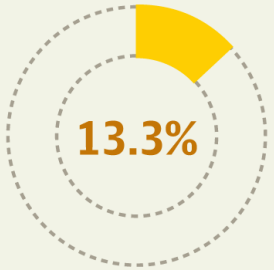
Cytisine

85 of 725 patients



Varenicline

97 of 727 patients



Cytisine was not noninferior to varenicline:

between-group difference, **−1.62%**
(1-sided 97.5% CI, −5.02% to ∞)

Courtney RJ, McRobbie H, Tutka P, et al. Effect of cytisine vs varenicline on smoking cessation: a randomized clinical trial. *JAMA*. Published July 6, 2021. doi:10.1001/jama.2021.7621

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for tobacco use cessation in people living with HIV (Review)

Mdege ND, Shah S, Dogar O, Pool ERM, Weatherburn P, Siddiqi K, Zyambo C, Livingstone-Banks J

Authors' conclusions

There is no clear evidence to support or refute the use of behavioural support over brief advice, one type of behavioural support over another, behavioural support plus NRT over behavioural support alone or brief advice, varenicline over NRT, or cytisine over NRT for tobacco use cessation for six months or more among PLWH. Nor is there clear evidence to support or refute the use of system-change interventions such as warm handoff over fax referral, to increase tobacco use cessation or receipt of cessation interventions among PLWH who use tobacco. However, the results must be considered in the context of the small number of studies included. Varenicline likely helps PLWH to quit smoking for six months or more compared to control. We did not find evidence of difference in SAE rates between varenicline and placebo, although the certainty of the evidence is low.

Cochrane Database of Systematic Reviews 2024, Issue 8. Art. No.: CD011120.

Clinical scores ”non-smoking” David

D:A:D Full model/Reduced model

D:A:D (R) CVD 5 and 10 year risk score

5 year
Reduced D:A:D result: 4.13%

10 year
Reduced D:A:D result: 8.38%

D:A:D (R) CVD 5 and 10 year risk score

5 year
Reduced D:A:D result: 2.34%

10 year
Reduced D:A:D result: 4.8%

ACC/AHA-ASCVD

8.6% Intermediate — Current 10-Year ASCVD Risk**

4.1% Low — Current 10-Year ASCVD Risk**

Framingham Heart Study (FHS-CVD)

11.5 %	10 %
10-year risk of MI or death for this patient	Average 10-year risk of MI or death

5.1 %	10 %
10-year risk of MI or death for this patient	Average 10-year risk of MI or death

ESC SCORE2 (SCORE2-OP)

5,7 %

10-year risk of CV event

3,2 %

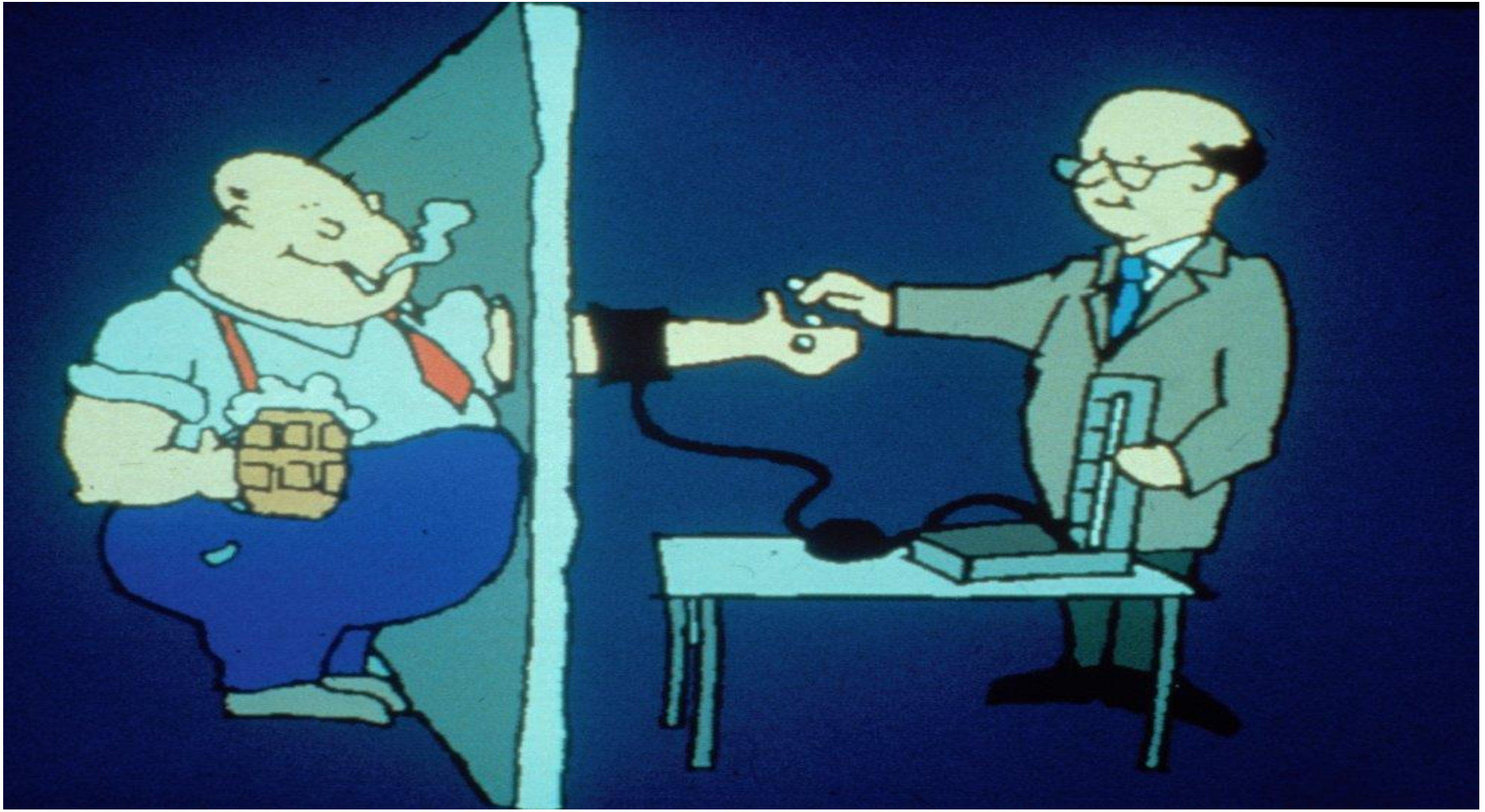
10-year risk of CV event

https://www.chip.dk/Resources/Clinical-risk-scores; https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ http://static.heart.org/riskcalc/app/index.html#!/baseline-risk). https://www.escardio.org/Education/ESCPrevention-of-CVDProgramme/Risk-assessment/esc-cvd-risk-calculation-app)

Take home messages

- PHIV are at an **increased risk** of cardiovascular disease. HIV (and ART?) contribute to cardiac risk along with the traditional host factors
- Currently available **risk scores** fail to accurately estimate (**underestimate**) CVR in HIV (but are the tool to be used!).
- **Smoking cessation**, dietary and exercise interventions are effective.
- **Statins** may be of benefit in addition to lipid lowering effects.

Quoting Dr. Gilleece:
“Make every contact count (YES, YES, YEES!)”



Thanks!

@adriacurran

adrian.curran@vallhebron.cat