Congresso Nazionale AGGIORNAMENTI INFETTIVOLOGICI: HIV, EPATITI & …..
Firenze, 15-17 Gennaio 2024

Effetti metabolici della ART

Paolo Maggi
Università della Campania, Luigi Vanvitelli
UOC Malattie Infettive e Tropicali AORN Caserta

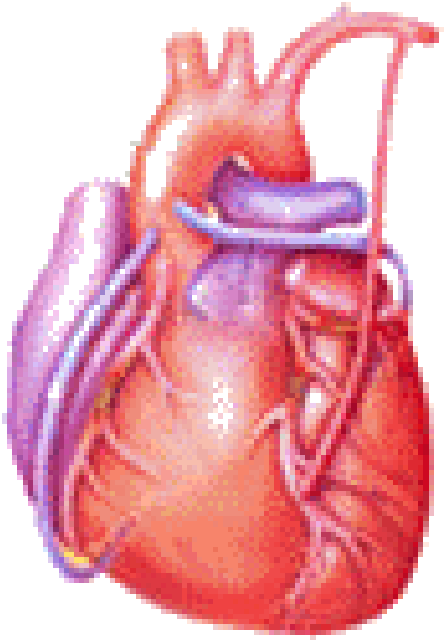
Il sottoscritto **prof. Paolo Maggi**
in qualità di docente

ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Grant for publication, Advisory board fees, Conference hospitality:	Gilead Science
Advisory board fees:	ViiV Healthcare
Advisory board fees, Conference hospitality:	MSD
Advisory board fees, Conference hospitality:	Janssen



GERVIH
Groupe d'Etude et de Recherche Ville-Hôpital

HIV Drug Therapy
GLASGOW 2022

O33

COCOVIH study: Over-mortality and impact of comorbidities for people living with HIV (PLHIV)

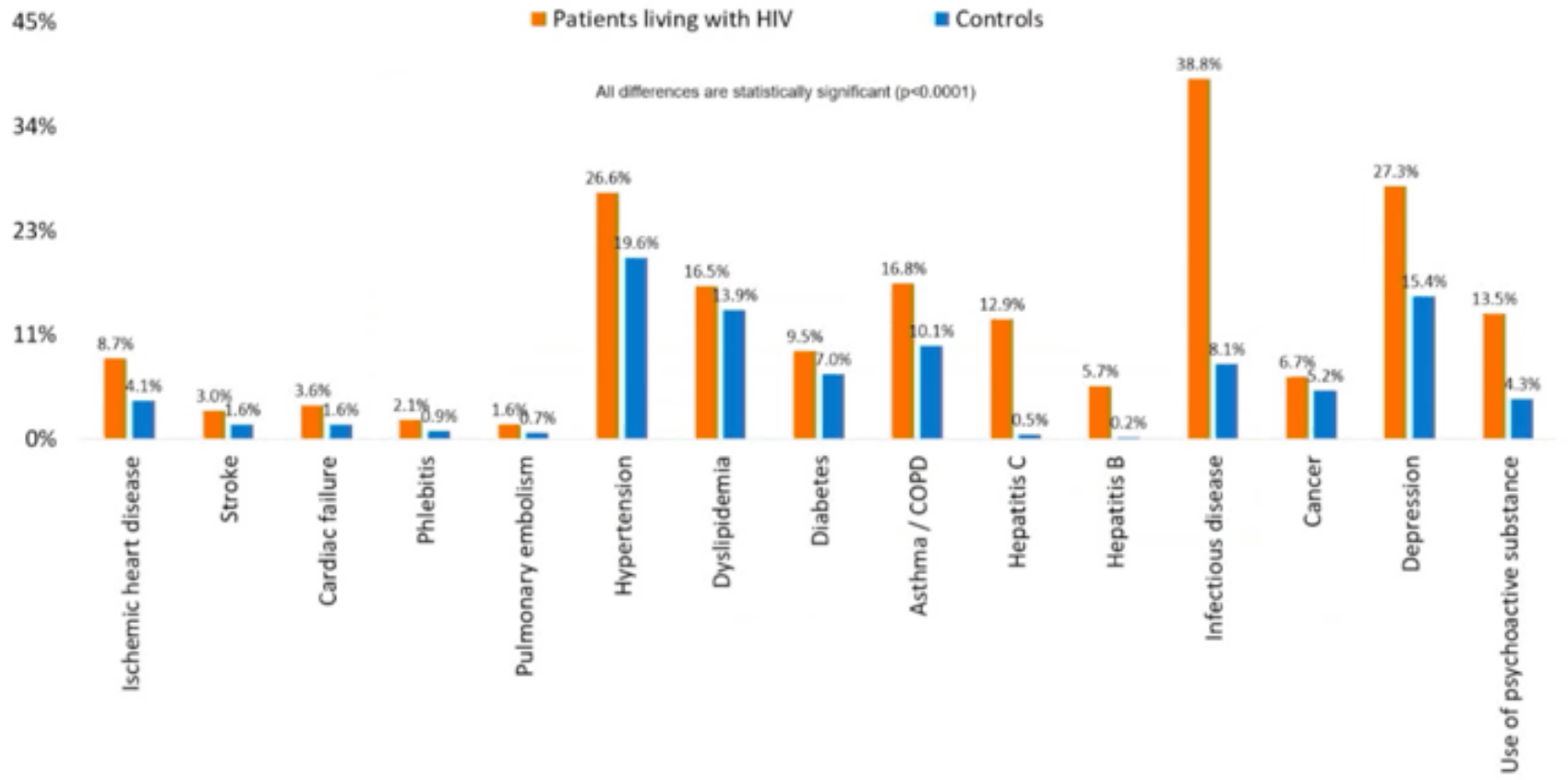
Prevoteau du Clary, François, Majerholc Catherine, Zucman David , Livrozet Jean Michel, Vallee Alexandre, Laurendeau Caroline, Bouee Stéphane

Hôpitaux de Toulouse
HOPITAL FOCH
HCL
CEMKA

Groupe — Control Group — PLHIV

COMORBIDITIES AND RISK FACTORS

PLHIV VERSUS FRENCH POPULATION



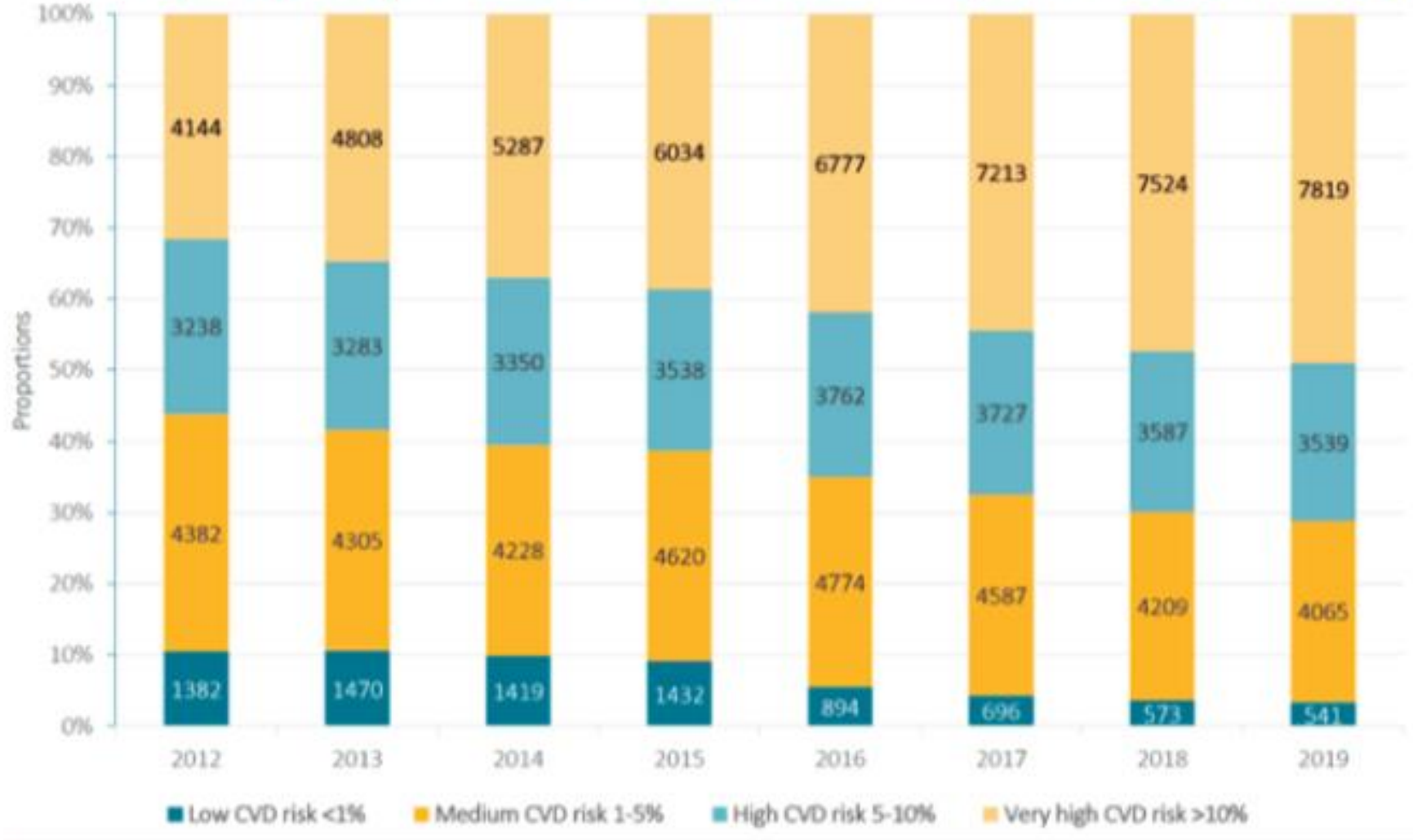
IMPACT of COMORBIDITIES on DEATHS

RESPOND International Cohort Consortium of Infectious Diseases

Use of Preventive Measures for Cardiovascular Disease in People Living with HIV

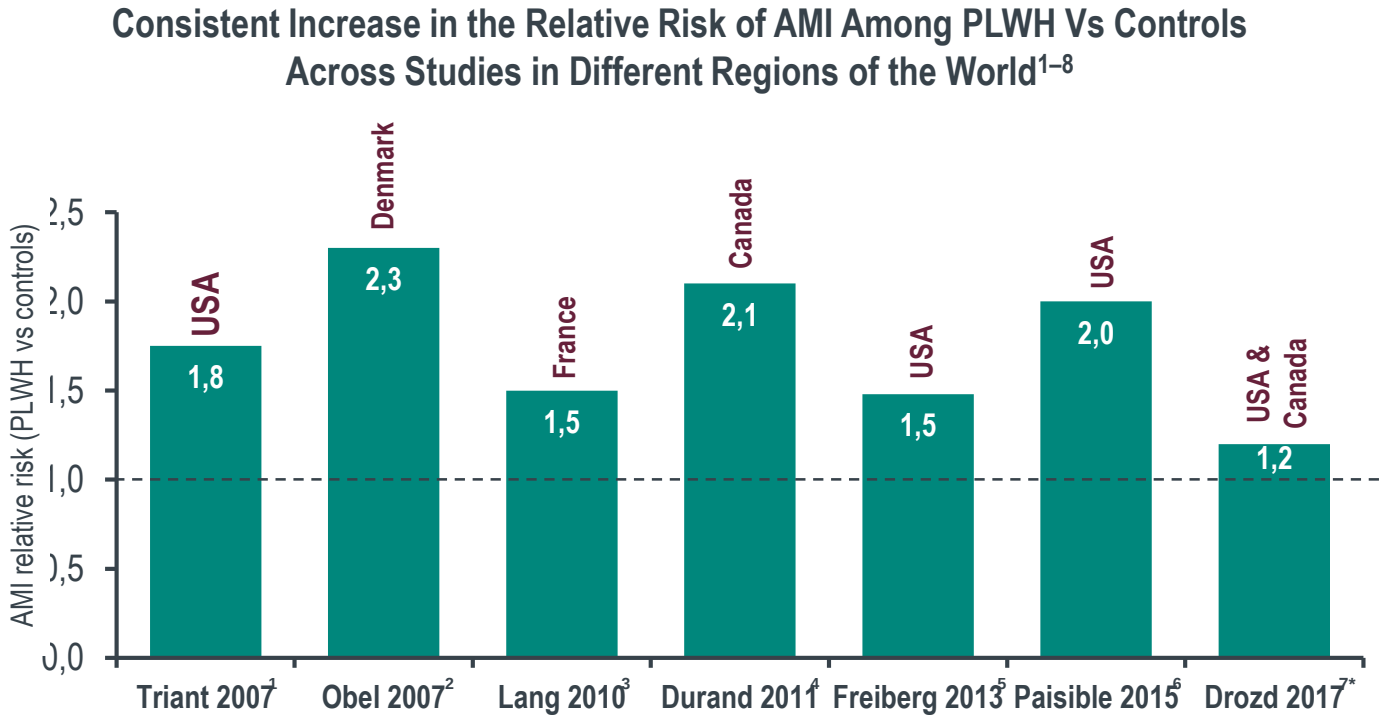
N. Jaschinski, B. Neesgaard, F. Wit, M. Van der Valk, H. Günthard, M. Stöckle, E. Wallner, J. Kowalska, A.L. Ridolfo, P. Nowak, A. Castagna, A. d'Arminio Monforte, N. Chkhartishvili, K. Petoumenos, J. Hoy, S. Hosein, H. Garges, J. Rooney, L. Young, J. Lundgren, L. Peters, A. Mocroft, and L. Ryom
for the RESPOND Study Group

Temporal Proportions of Estimated 10-year CVD Risk



While participants were not allowed to switch CVD risk groups, the proportion of **very high estimated CVD risk** individuals increased in 2019 **(49%)** vs 2012 **(31.5%)**

Globally, CVD is a Leading Concern for PLWH



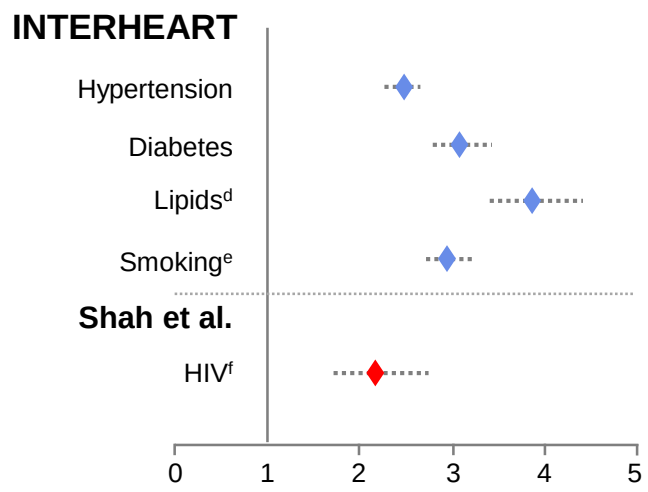
*Type 1 myocardial infarction events.

1. Triant VA, et al. *J Clin Endocrinol Metab* 2007;92:2506–12; 2. Obel N, et al. *Clin Infect Dis* 2007;44:1625–31; 3. Lang S, et al. *AIDS* 2010;24:1228–30; 4. Durand M, et al. *J Acquir Immune Defic Syndr* 2011;57;245–53; 5. Freiberg MS, et al. *JAMA Intern Med*. 2013;173:614–22; 6. Paisible AL, et al. *J Acquir Immune Defic Syndr* 2015;68:209–16; 7. Drozd DR, et al. *J Acquir Immune Defic Syndr* 2017;75:568–76.

CVD Risk Reported to be Twice as High in PLWH

Results of a systematic meta-analysis >790,000 PLWH reported a pooled RR of incident CVD of 2.16 (95% CI, 1.68–2.77), which is within the range of traditional CV risk factors[1,2]

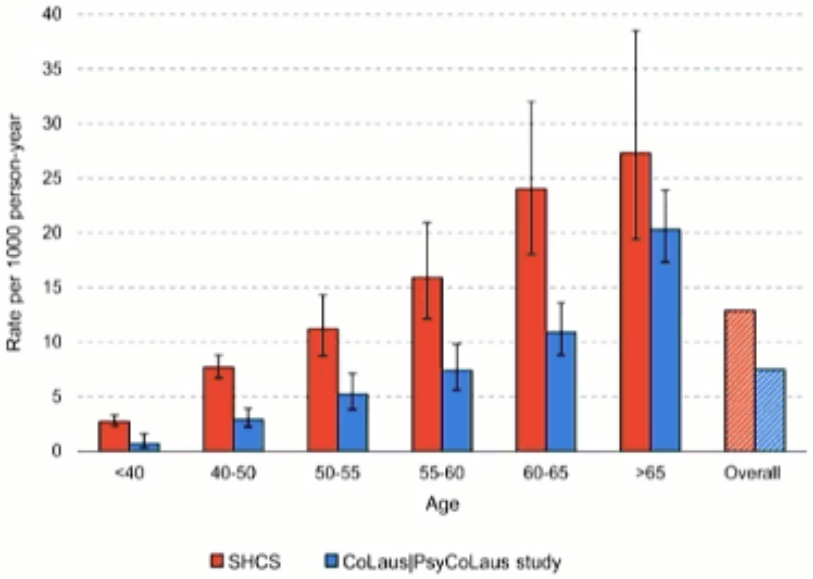
CV risk of HIV compared to TRF[2,a]



	OR (99% CI)[b]	PAR
Hypertension	2.48 (2.30-2.68)	23.4%
Diabetes	3.08 (2.77-3.42)	12.3%
Lipids[d]	3.87 (3.39-4.42)	54.1%
Smoking[e]	2.95 (2.72-3.20)	36.4%
	RR (95% CI)[c]	**PAR**
HIV[f]	2.16 (1.68-2.77)	0.92%

TRF=traditional risk factors.
[a]Because odds ratios can give inflated estimates of risk when the outcome is common, it is likely that the RRs of traditional risk factors in the INTERHEART study are smaller and thus closer to that of HIV.
[b]Risk of acute MI, adjusted for age, sex, and smoking. Adjustment for confounders was limited to those available in the primary studies. [c]Risk of ASCVD (CVD, stroke, or MI). [d]High ApoB/ApoA1 ratio. [e]OR (99% CI) for current smoking; PAR for any smoking. [f]PAR for 2015 using prevalence data for HIV for the 15- to 49-year-old group. Apo indicates apolipoprotein.
ASCVD, atherosclerotic cardiovascular disease; OR, odds ratio; PAR, population attributable risk; and RR, risk ratio.
1. Shah ASV et al. *Circulation*. 2018;138 (11):1100-1112. **2.** Hsue P et al. *Circulation.* 2018;138 (11):1113-1115.

6373 PWH (SHCS) and **5403** from the general population (CoLaus|PsyCoLaus)



PWH had a **two-fold higher rate** of cardiovascular disease events compared with the general population

Delabays et al. Eur J Prev Cardiol. 2022

EACS 2023 Oct 19

Subclinical coronary artery disease in persons living with HIV and uninfected controls: PWH at 2-3 fold higher risk

Andreas Dehlbæk Knudsen, MD, PhD

To compare subclinical CAD in PLWH and uninfected controls from the background population using coronary CT angiography (CCTA)

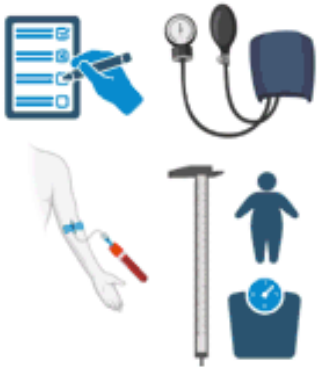
To determine if HIV serostatus is independently associated with CAD and adverse plaque features including non-calcified plaque.

Methods

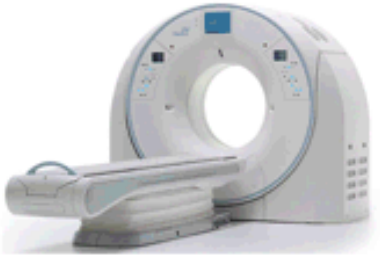
Inclusion criteria
- No known CAD
- Older than 40 years of age

Same protocol
- Questionnaires
- Blood pressure
- Anthropometry
- Blood samples
- Coronary CT angiography

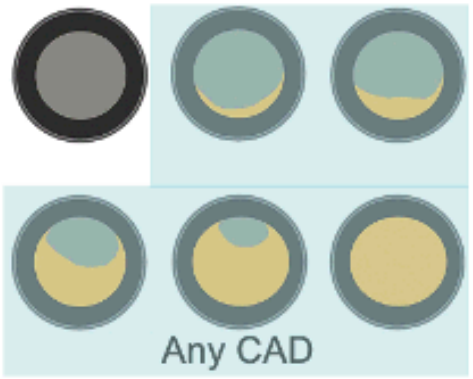
PLWH
COCOMO study



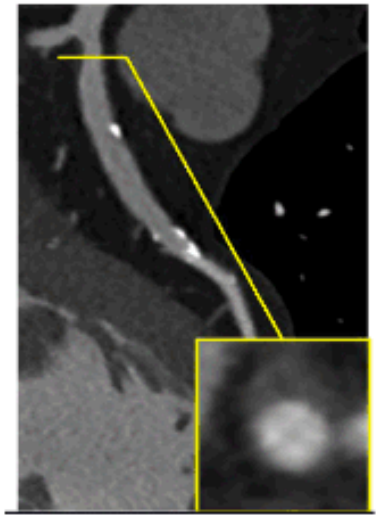
Non-HIV infected individuals
Copenhagen general population study



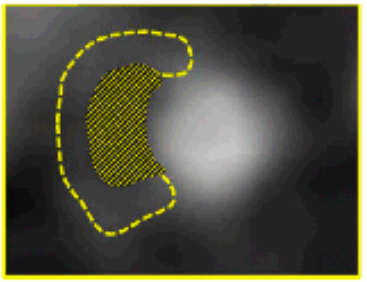
Methods – Outcome definitions



≥50% stenosis

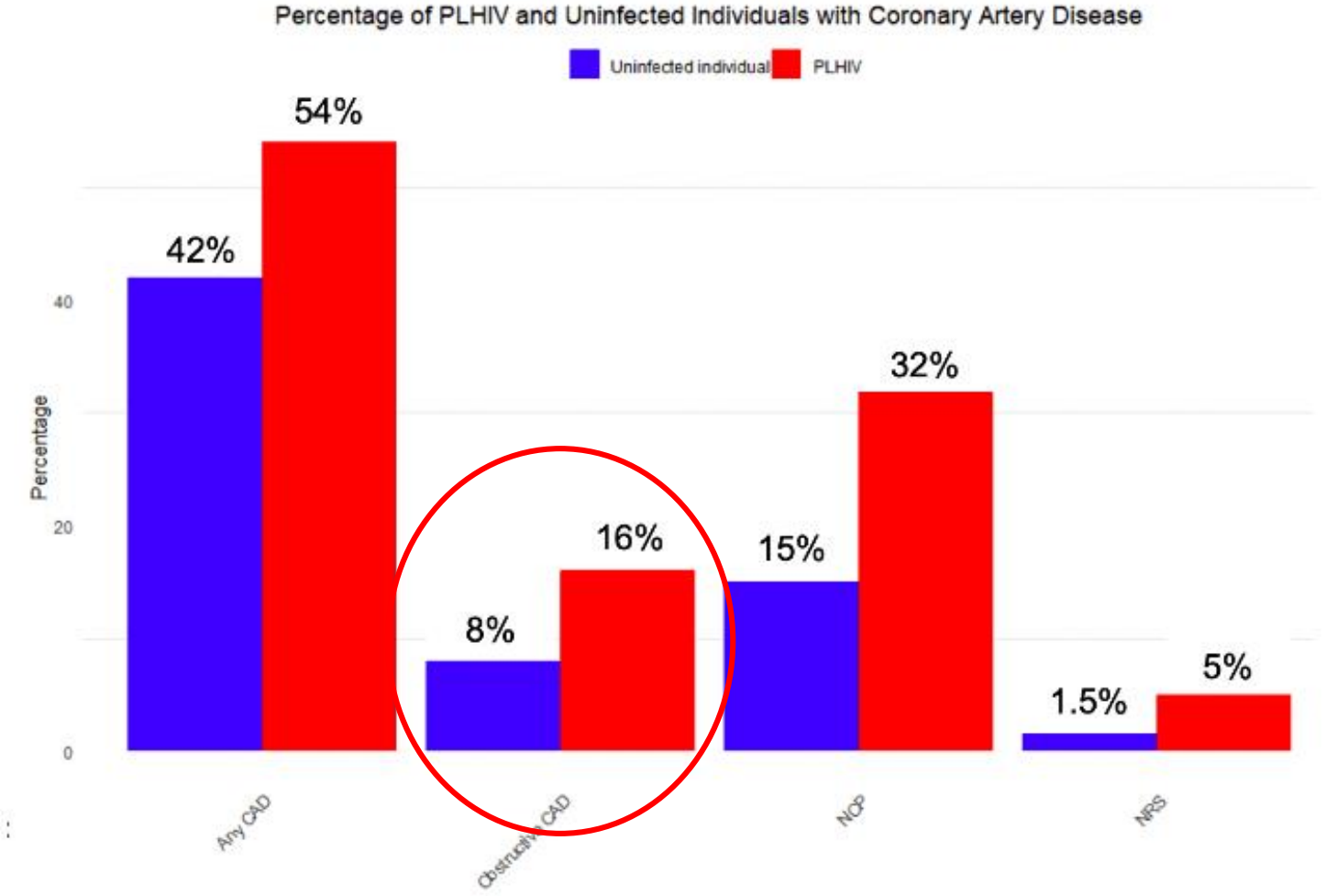


Non-Calcified plaque



Napkin Ring Sign

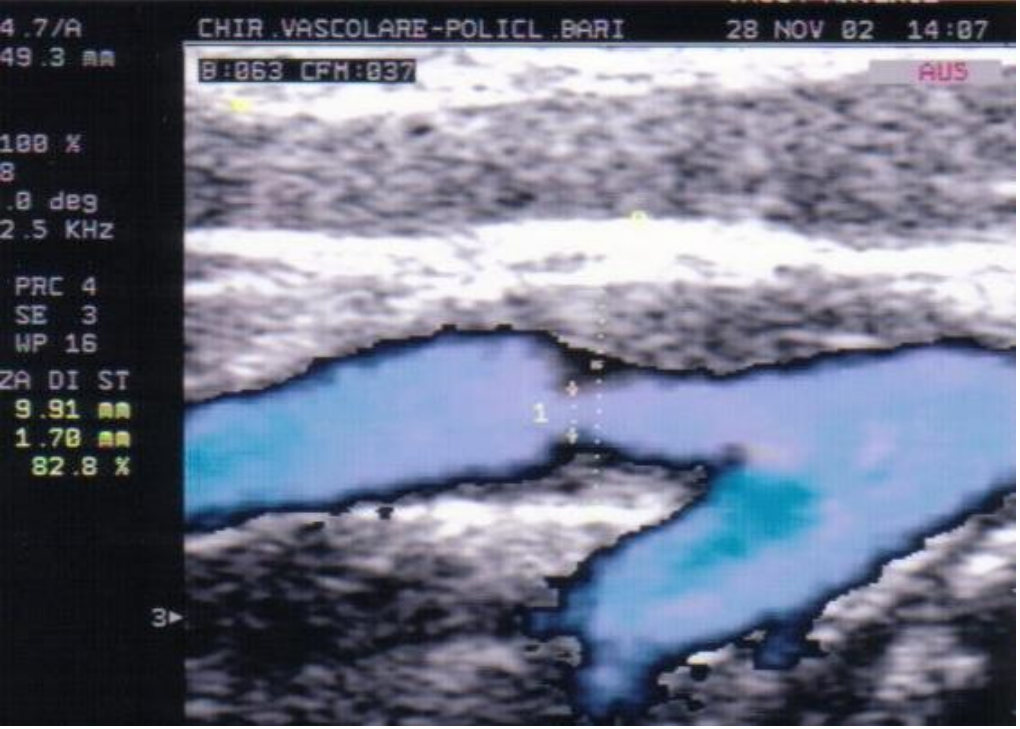
Results


Percentage of PLHIV and Uninfected Individuals with Coronary Artery Disease
Uninfected individual
PLHIV
Percentage
40
20
0
42%
54%
8%
16%
15%
32%
1.5%
5%
Any CAD
Obstructive CAD
NOP
NRS

Conclusions:

Among individuals aged ≥40 without known CAD

- PLWH have 2-fold higher odds of obstructive CAD compared to age- and sex matched uninfected individuals.
- HIV positive serostatus is associated with 3-fold higher odds of obstructive CAD after adjusting for risk factors
- HIV positive serostatus is associated with higher odds of adverse plaque features among individuals with CAD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100 %
8
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SE 3
WP 16
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9.91 mm
1.70 mm
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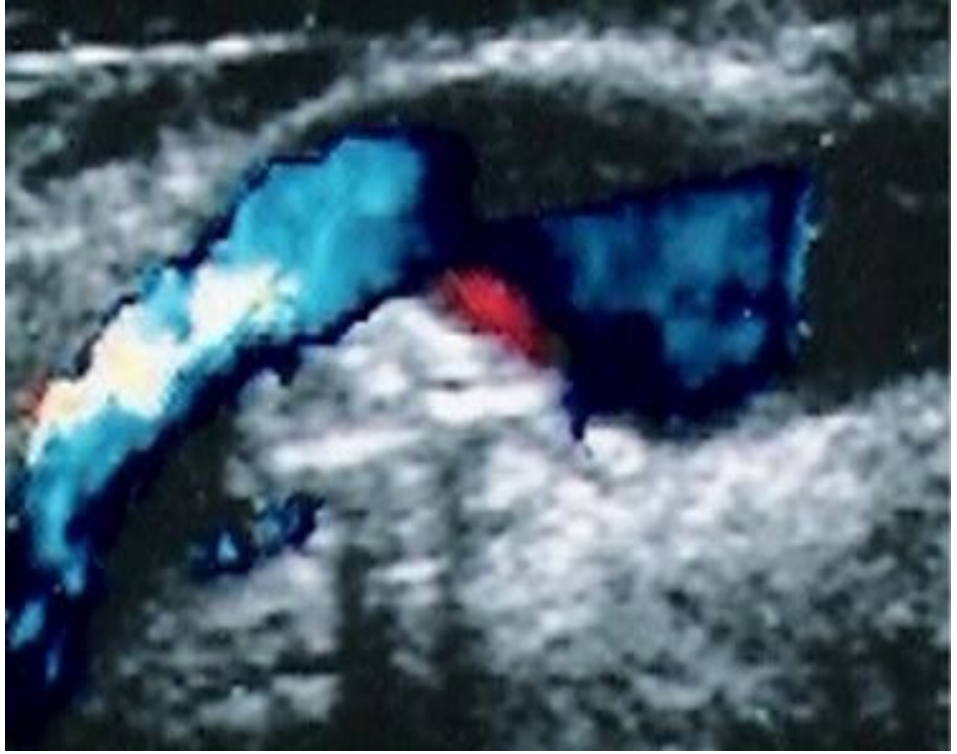

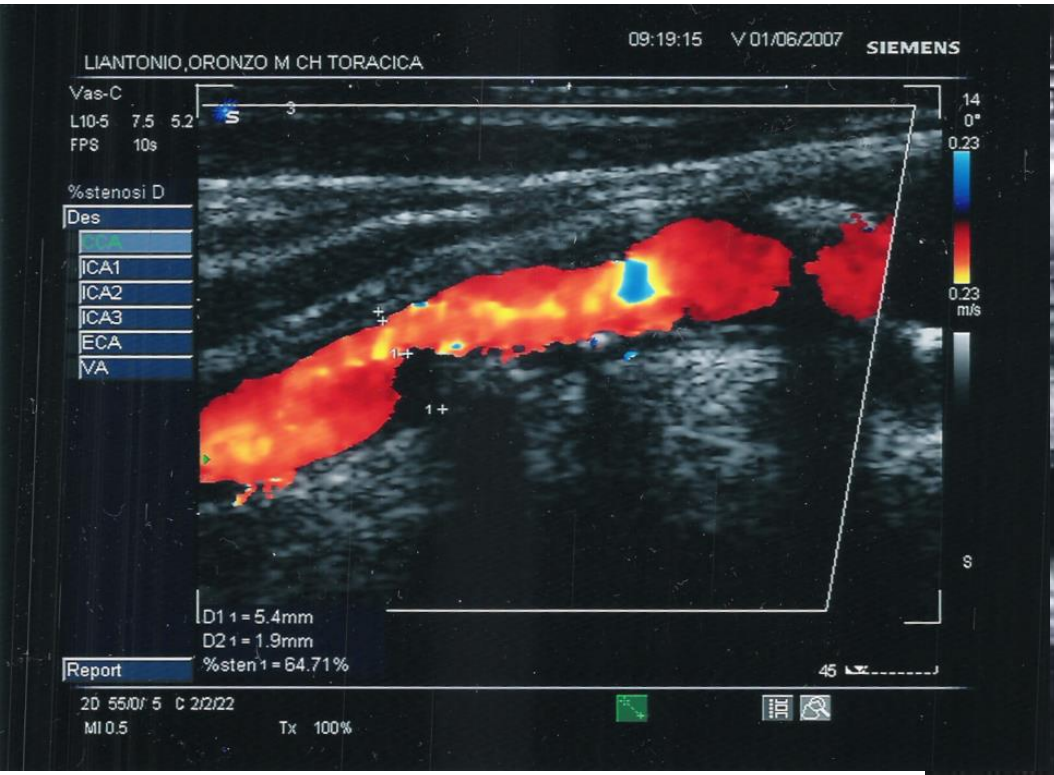
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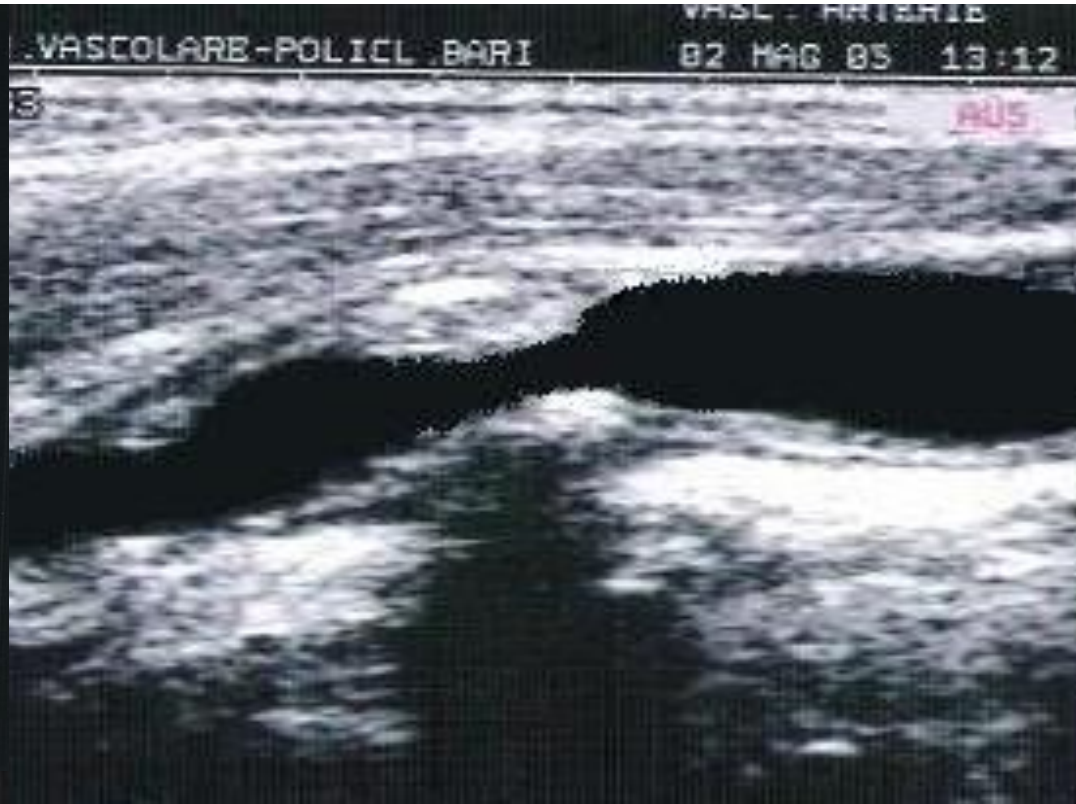
Tx 100%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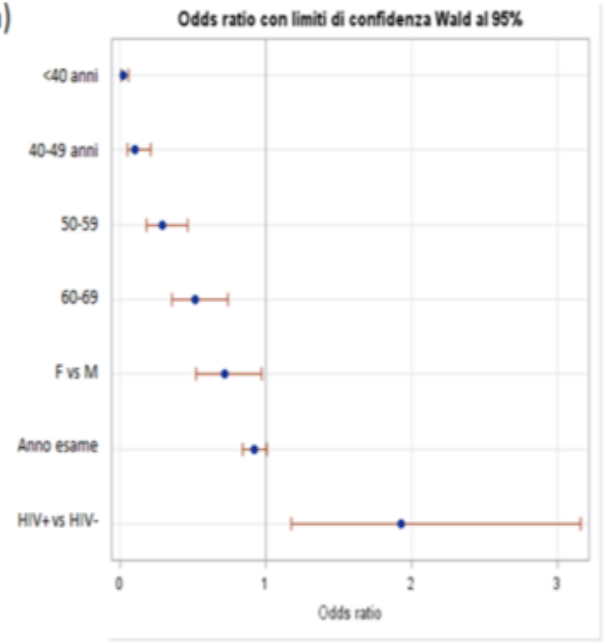
Martini S. et al.

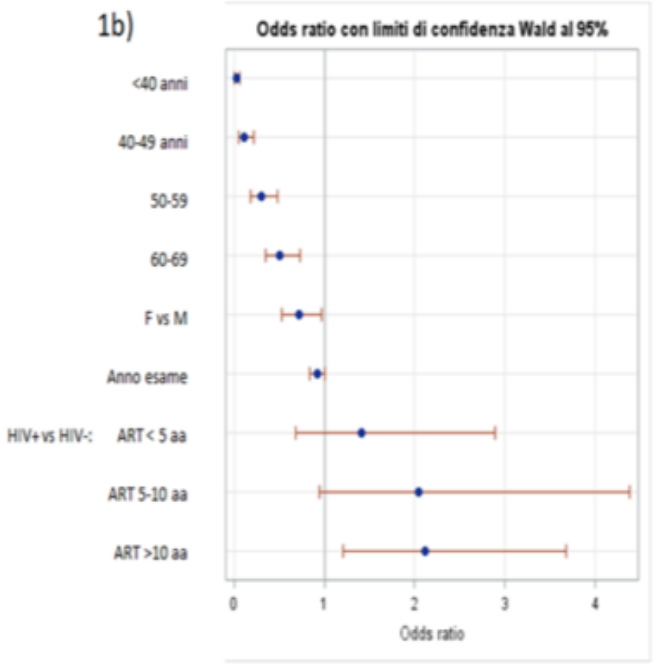
Valutazione dello spessore miointimale e delle placche ateromasiche in pazienti con infezione da HIV experienced vs pazienti HIV negativi: dati della coorte Archiprevaleat

Conclusioni: In conclusione, i nostri dati in real-life, sebbene parziali, mostrano che i pazienti HIV+, trattati con regimi antiretrovirali, sono più a rischio di sviluppare IMT e placche ateromasiche rispetto ai soggetti HIV-. Lo sono in misura maggiore se sono trattati da più tempo e se hanno età più avanzata. Questo può stimolare a migliorare il monitoraggio dei pazienti con il doppler per prevenire il rischio cardiovascolare che è una delle principali cause di decesso dei pazienti HIV+.

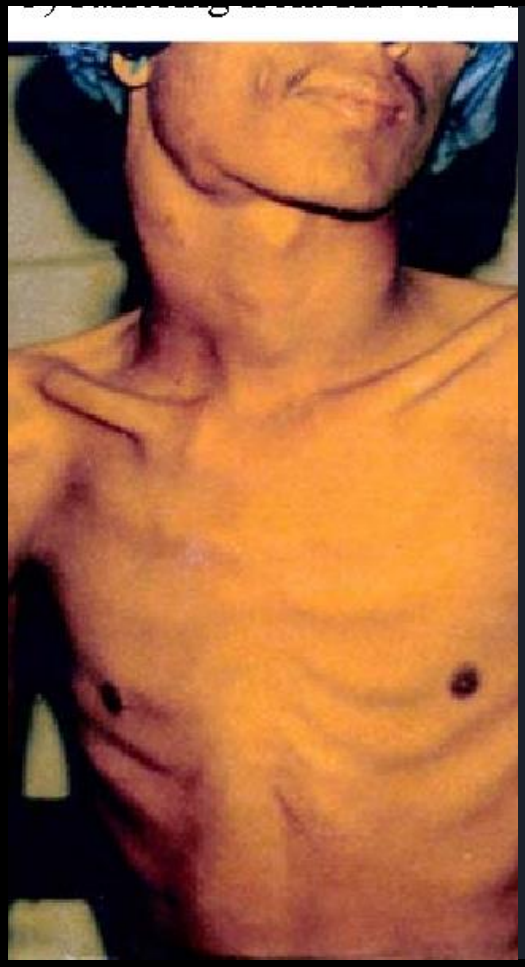
1a)



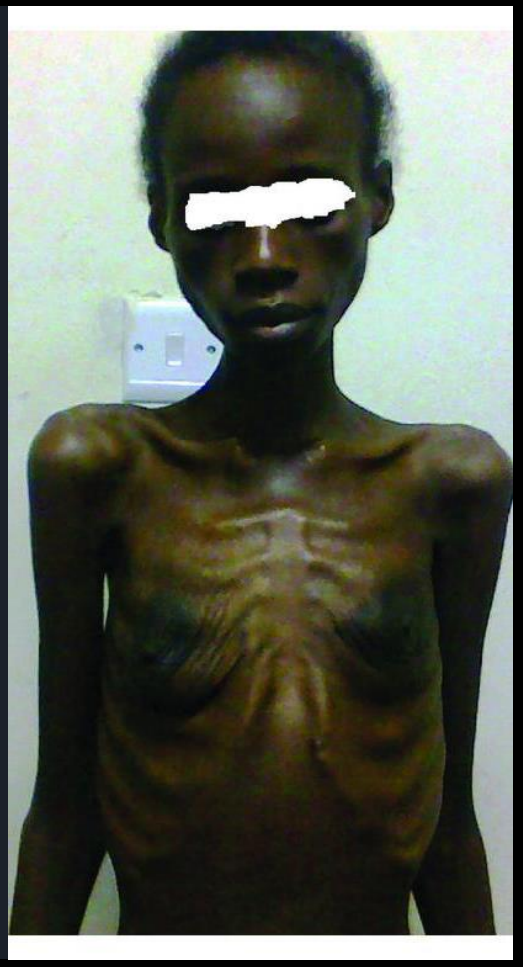
1b)



Weight gain

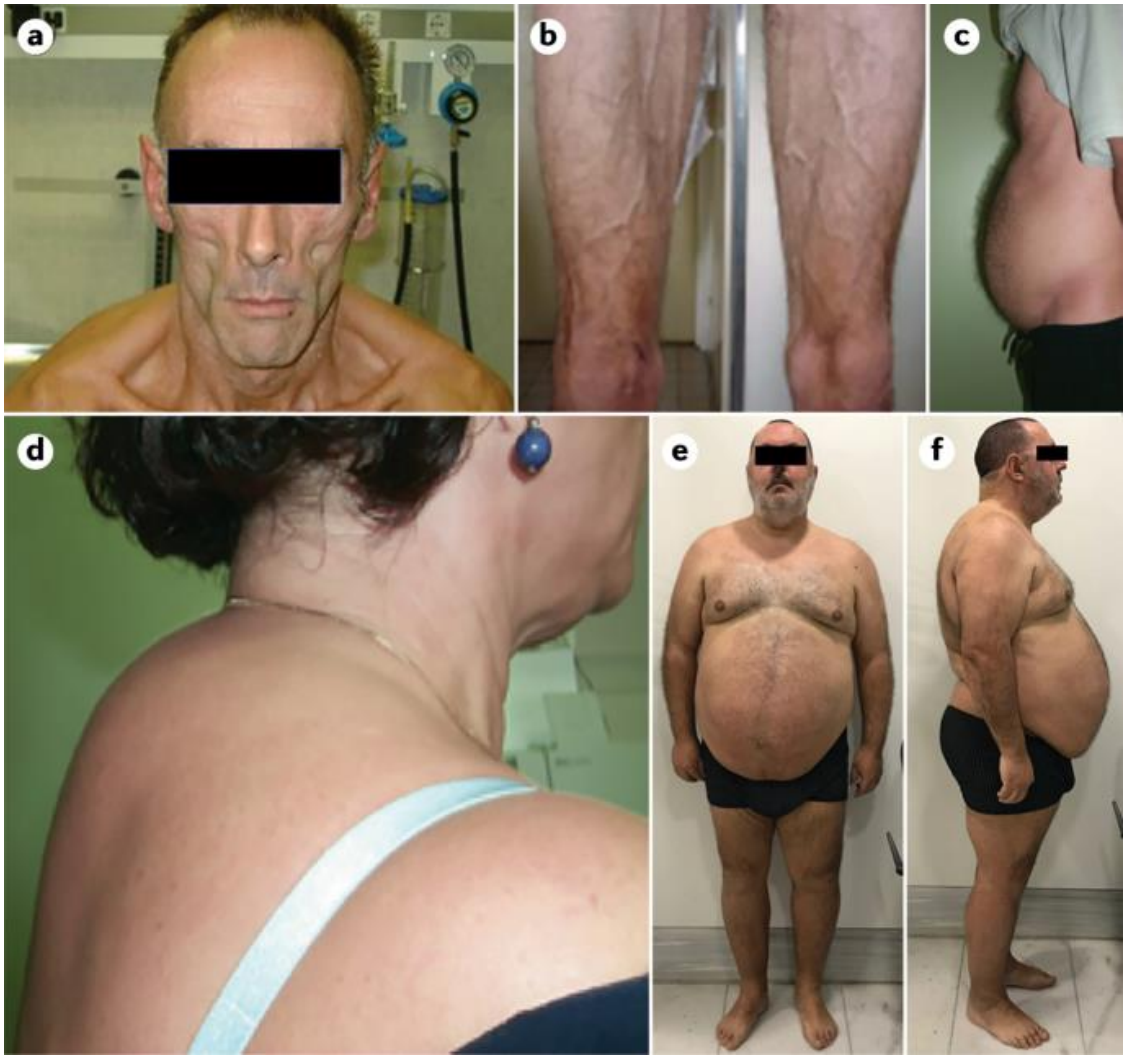


Pre-ART ERA:
wasting syndrome

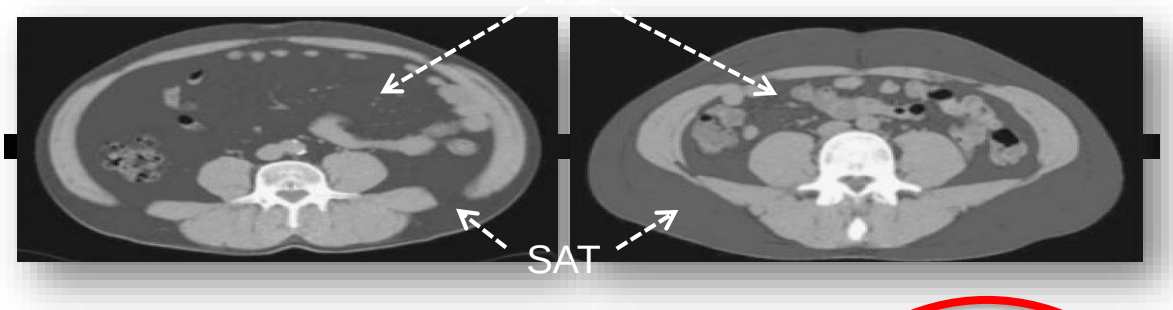


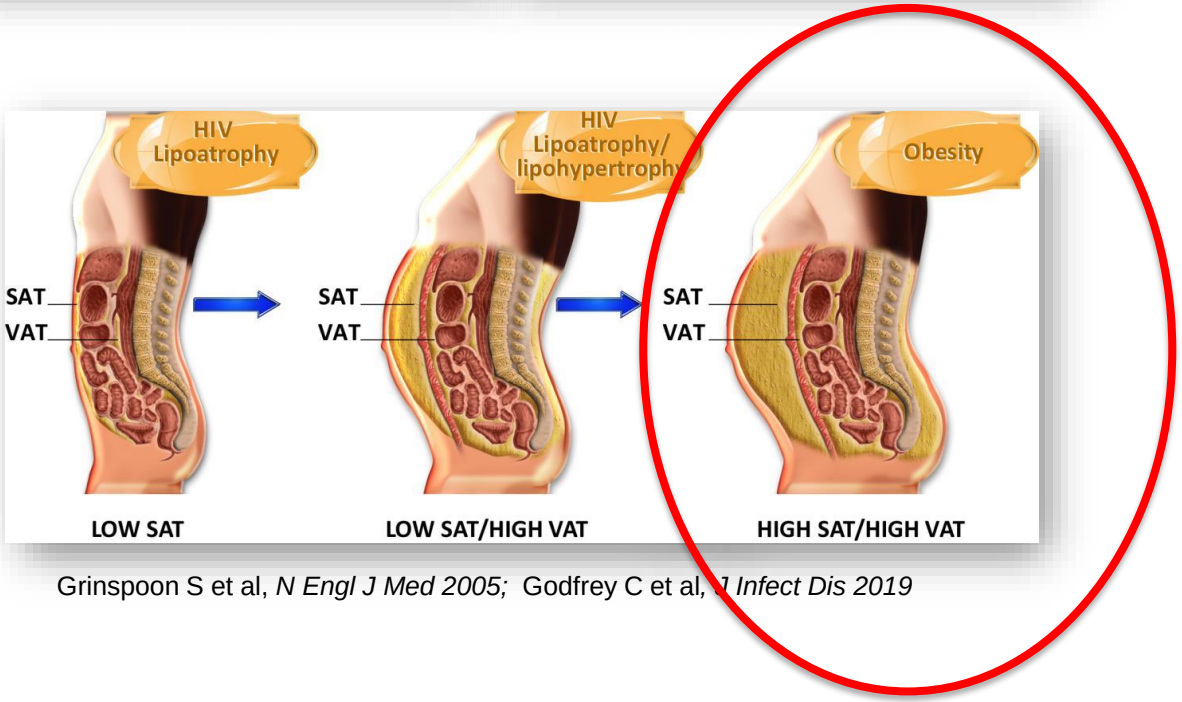
CISAI
FONDAZIONE ASIA

Old and new ARVs



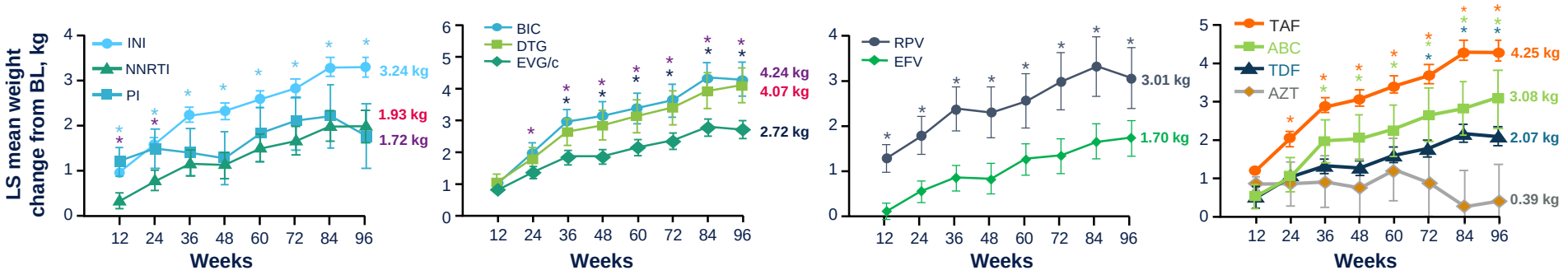
Body-Fat Abnormalities in HIV-Infected Adults





Grinspoon S et al, *N Engl J Med 2005;* Godfrey C et al, *J Infect Dis 2019*

- **Pooled analysis of eight RCTs of treatment-naïve PLHIV (N=5,680)**

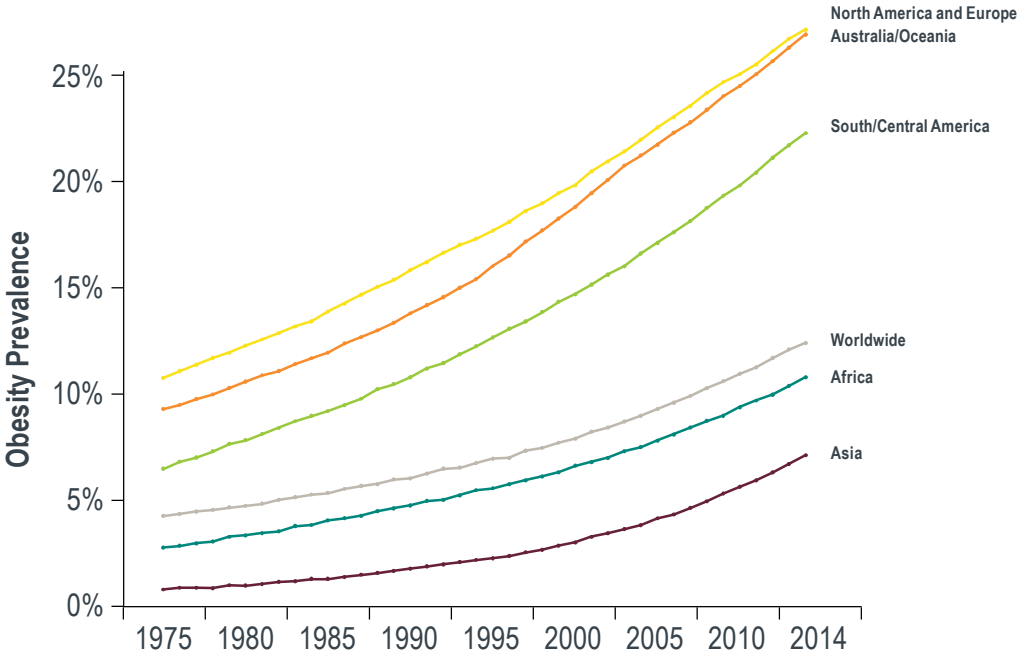


Risk factor for significant (≥10%) weight gain	OR (95% CI)	p value
BIC/DTG vs EFV	1.82 (1.24, 2.66)	0.002
EVG/c vs EFV	1.36 (1.04, 1.78)	0.026
RPV vs EFV	1.51 (1.03, 2.20)	0.035
ATV/r vs EFV	0.92 (0.59, 1.45)	0.73
TAF vs AZT	1.75 (1.04, 2.95)	0.034
TAF vs ABC	1.90 (1.25, 2.88)	0.003
TAF vs TDF	1.47 (1.14, 1.90)	0.003

Obesity Prevalence is Increasing Worldwide

BMI Category	BMI Value
Underweight	< 18.5
Normal	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	> 30.0

- ***Global increase over past 3 decades[2]***



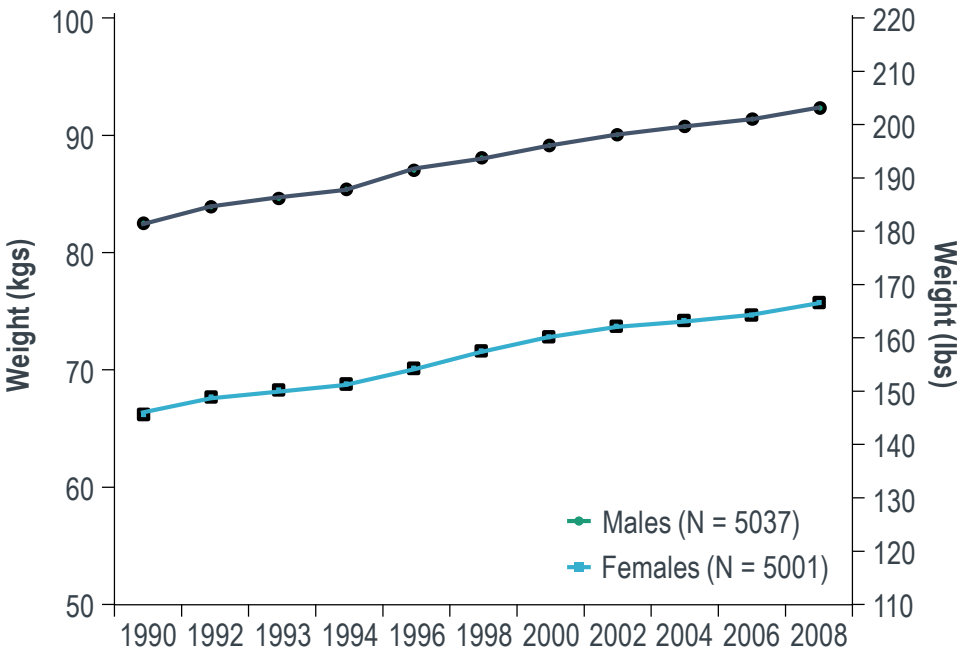
In 2015-2016, ~70% of adults aged 20 and over in the United States were overweight or obese[1]

1. CDC. National Center for Health Statistics. Obesity and Overweight. https://www.cdc.gov/nchs/fastats/obesity-overweight.htm. Accessed 11-Dec-2019
2. National Academies of Sciences, Engineering, and Medicine. 2019. Current Status and Response to the Global Obesity Pandemic: Proceedings of a Workshop. Washington, DC: The National Academies Press.

In the general population, studies have shown an average weight gain of 0.5 kg (1.2 lb) per year

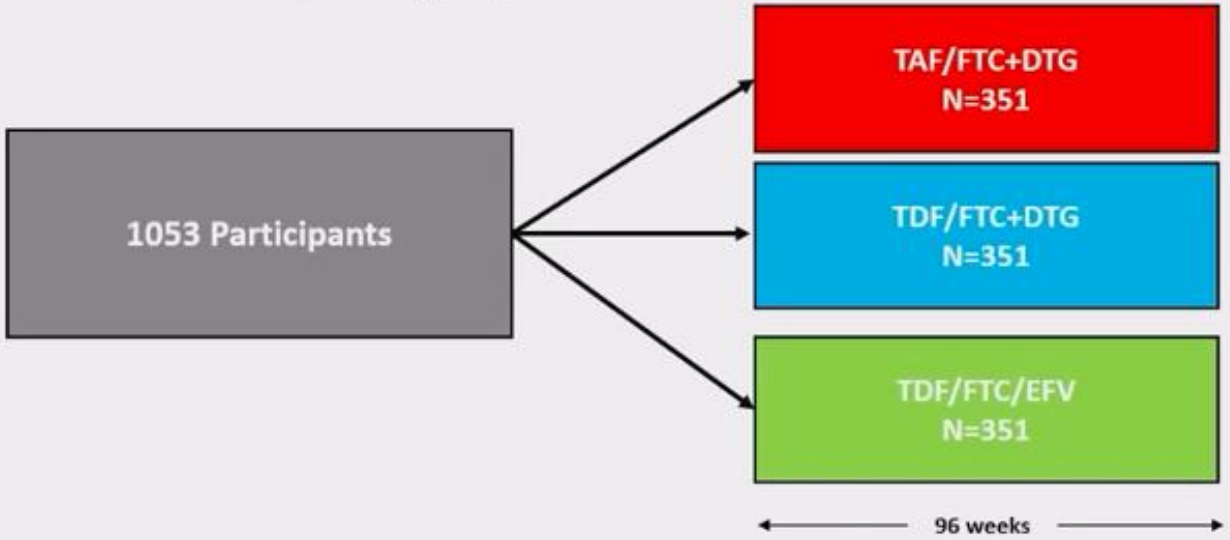
- **Weight gain over an 18-year (1990-2008) follow-up period was assessed in a nationally representative cohort of 10,295 US adults (mean age at baseline 29.2 ± 0.03)[1a]**
  - Study population included 79% non-Black (non-Hispanic), 14% Black, and 7% Hispanic
  - Individuals generally shifted into a higher BMI category by middle age
  - Average weight gain over the follow-up period was 9-10 kg
    - This corresponds to a BMI increase in men of 3.1 kg/m^2 (12% from BL) and in women 3.5 kg/m^2 (14% from BL)
  - Early and rapid weight gain increased the risk for obesity-related conditions

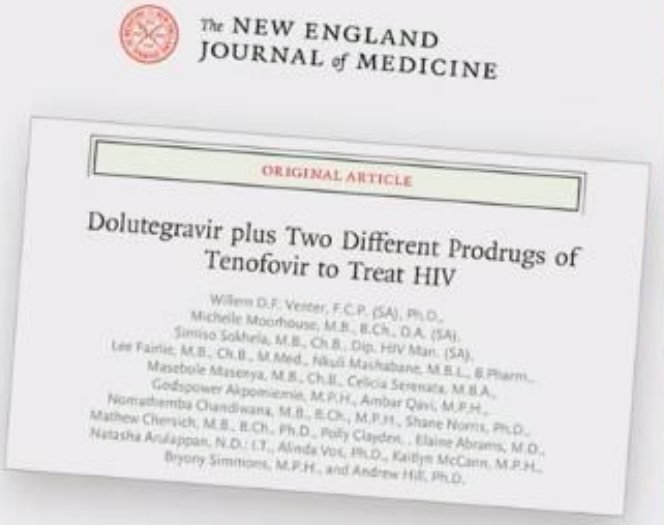
Average weight over time for men and women in the general population



ADVANCE: Study design

Inclusion criteria: treatment-naïve, HIV-1 RNA level ≥ 500 copies/mL, no TB or pregnancy, no baseline genotyping




The NEW ENGLAND JOURNAL of MEDICINE

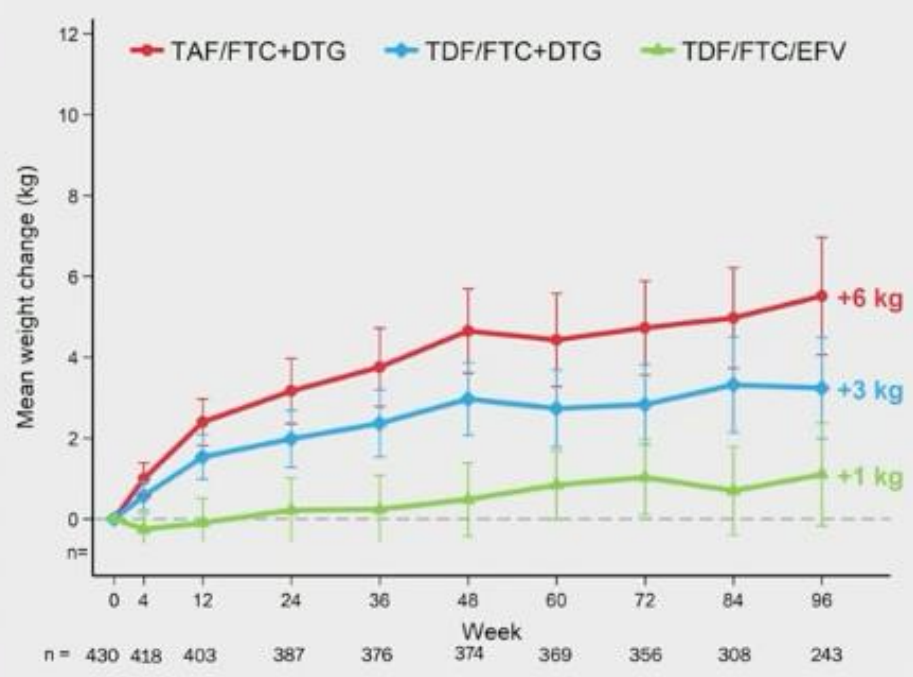
ORIGINAL ARTICLE

Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV

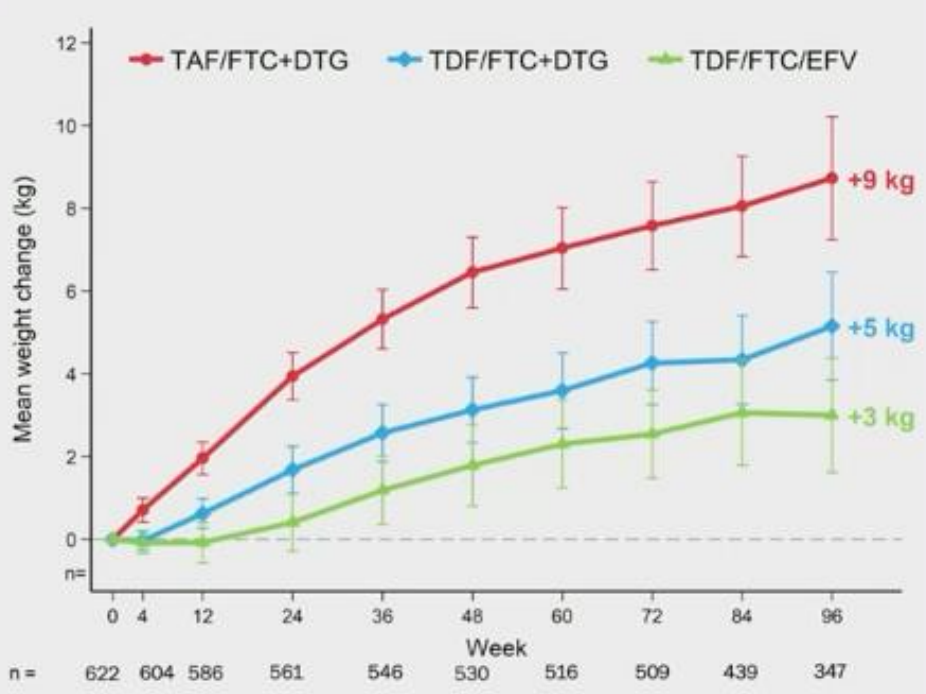
Willem D.F. Venter, F.C.P. (SA), Ph.D., Michelle Moorhouse, M.B., B.Ch., D.A. (SA), Simiso Sokhela, M.B., Ch.B., Dip. HIV Man. (SA), Lee Fairlie, M.B., Ch.B., M.Med., Nkuli Mashabane, M.B.L., B.Pharm., Masebole Maseriya, M.B., Ch.B., Celicia Serenata, M.B.A., Godspower Akpomiemie, M.P.H., Ambar Qavi, M.P.H., Nomathemba Chandiwana, M.B., B.Ch., M.P.H., Shane Norris, Ph.D., Mathew Chersich, M.B., B.Ch., Ph.D., Polly Clayden, , Elaine Abrams, M.D., Natasha Arulappan, N.D., I.T., Alinda Vos, Ph.D., Kaitlyn McCann, M.P.H., Bryony Simmons, M.P.H., and Andrew Hill, Ph.D.

Open-label, 96-week study in Johannesburg, South Africa
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84, and 96

Mean change in weight (kg) to Week 96



MEN

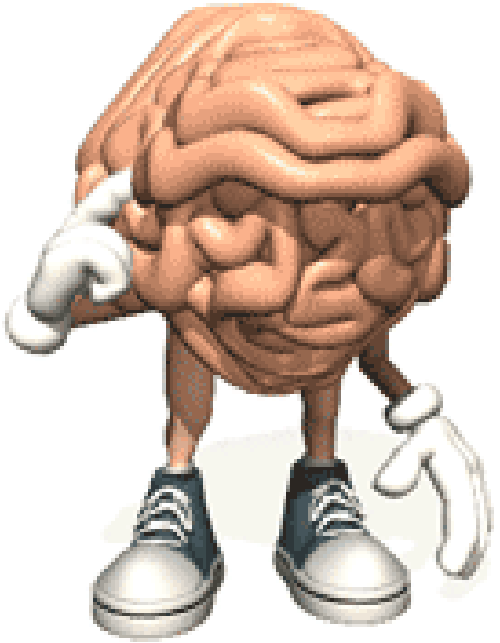


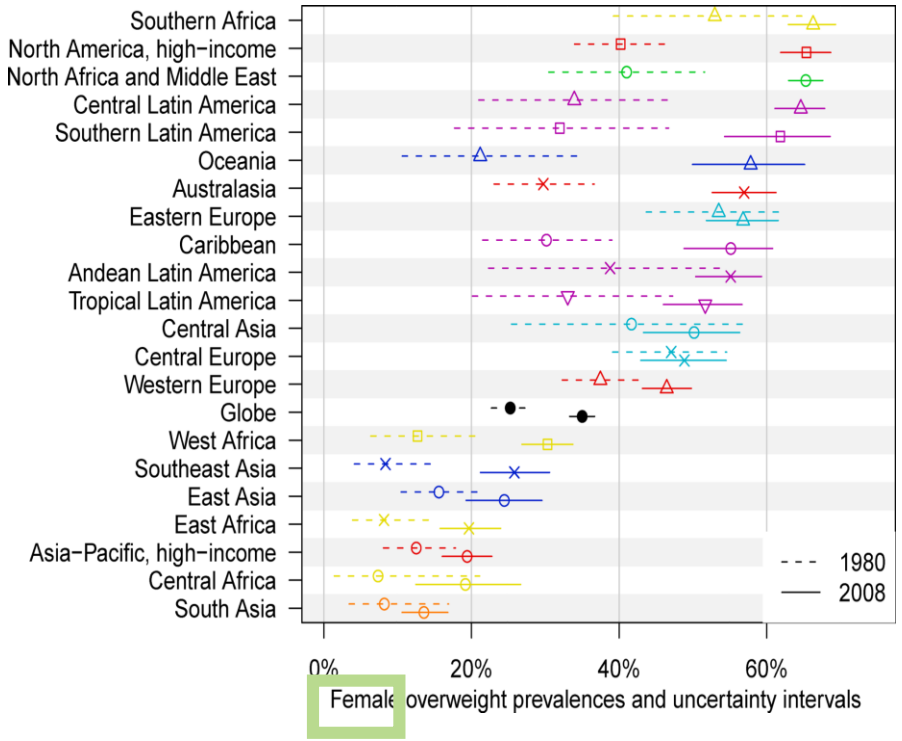
WOMEN

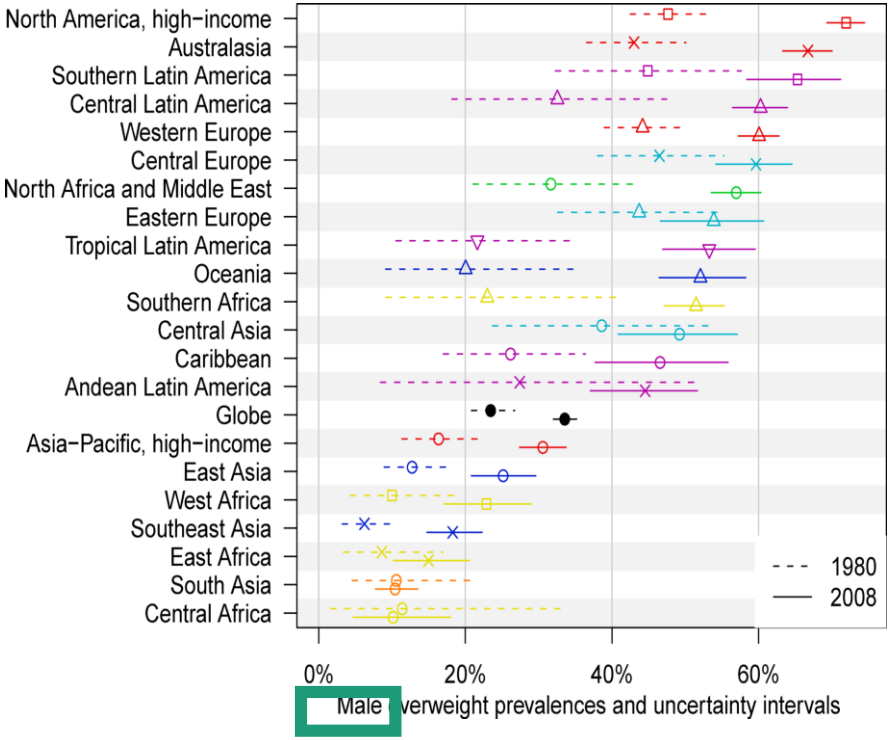
Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC or TDF/FTC or TDF/3TC + DTG		III (Weight increase (DTG, TAF)) IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC/BIC		II (Weight increase (BIC))
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (RAL: dosing)
1 NRTI + INSTI		
3TC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL	

EACS guidelines

Molti dubbi….



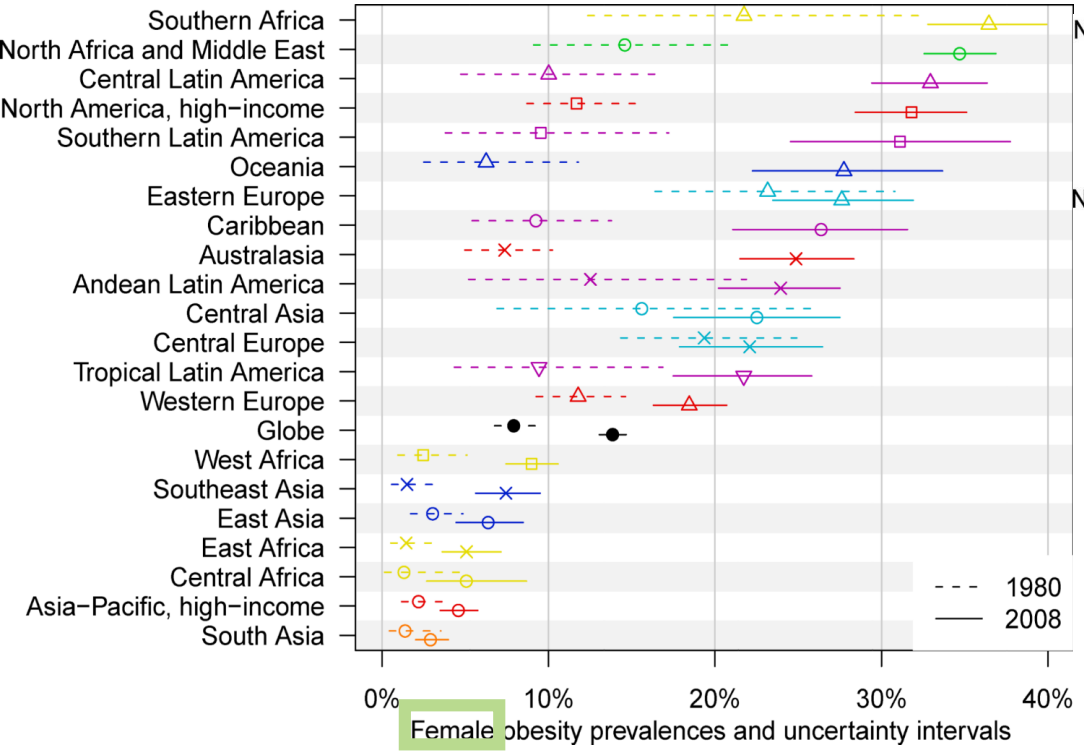


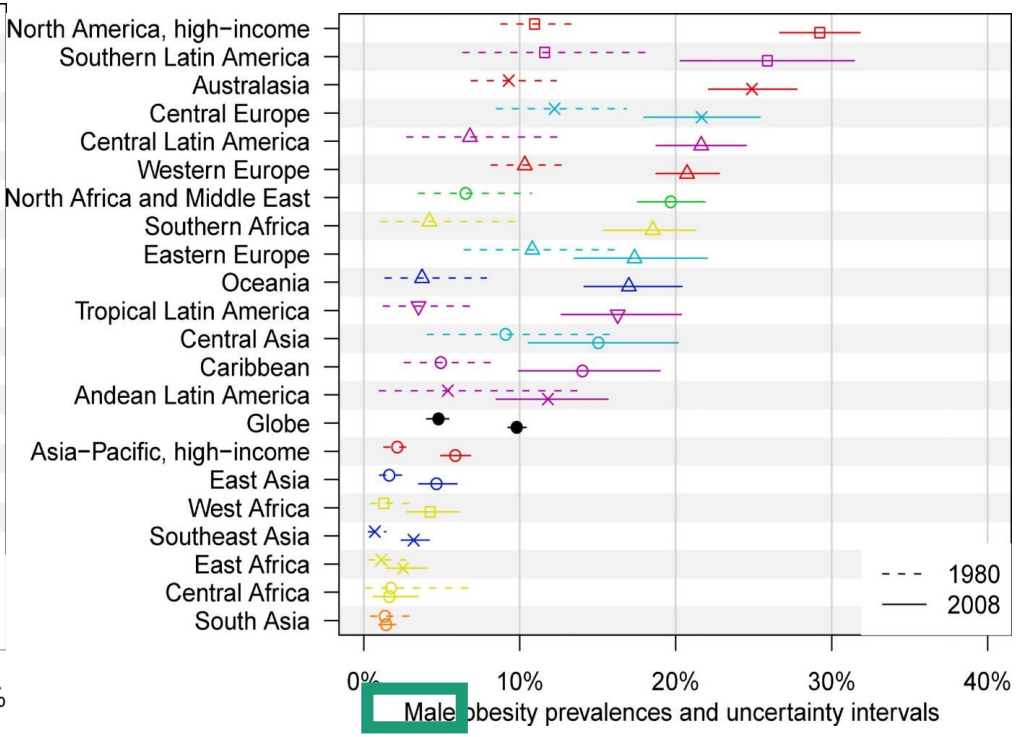


The epidemiology is changing...

OVERWEIGHT

Finucane M, et al. Lancet 2011;377:557–567





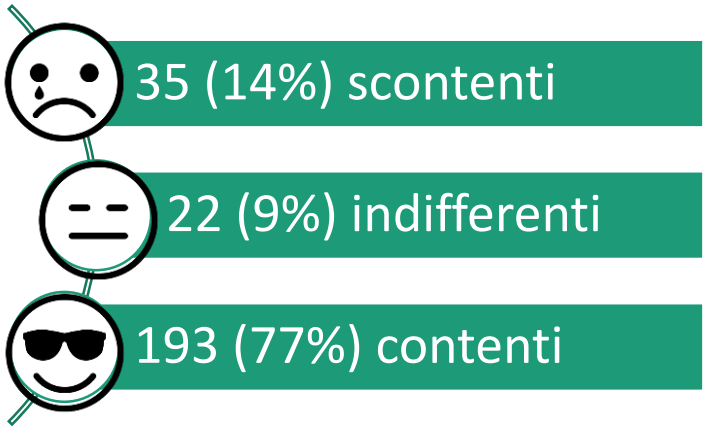
The epidemiology is changing...

OBESITY

Finucane M, et al. Lancet 2011;377:557–567

ADVANCE: percezione dell'aumento di peso

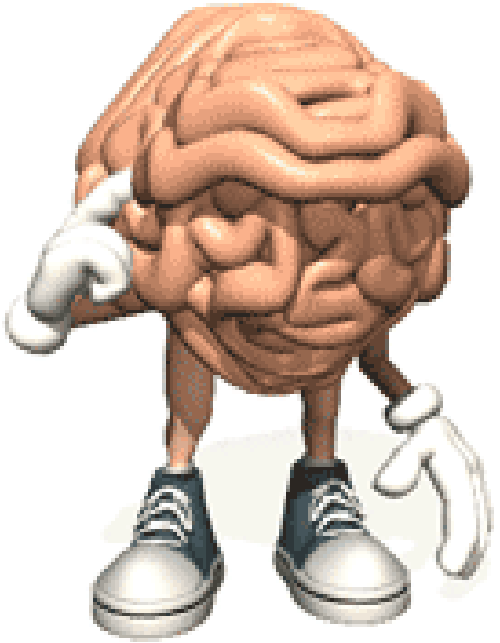
- 250 persone intervistate (150 femmine, 93 maschi)



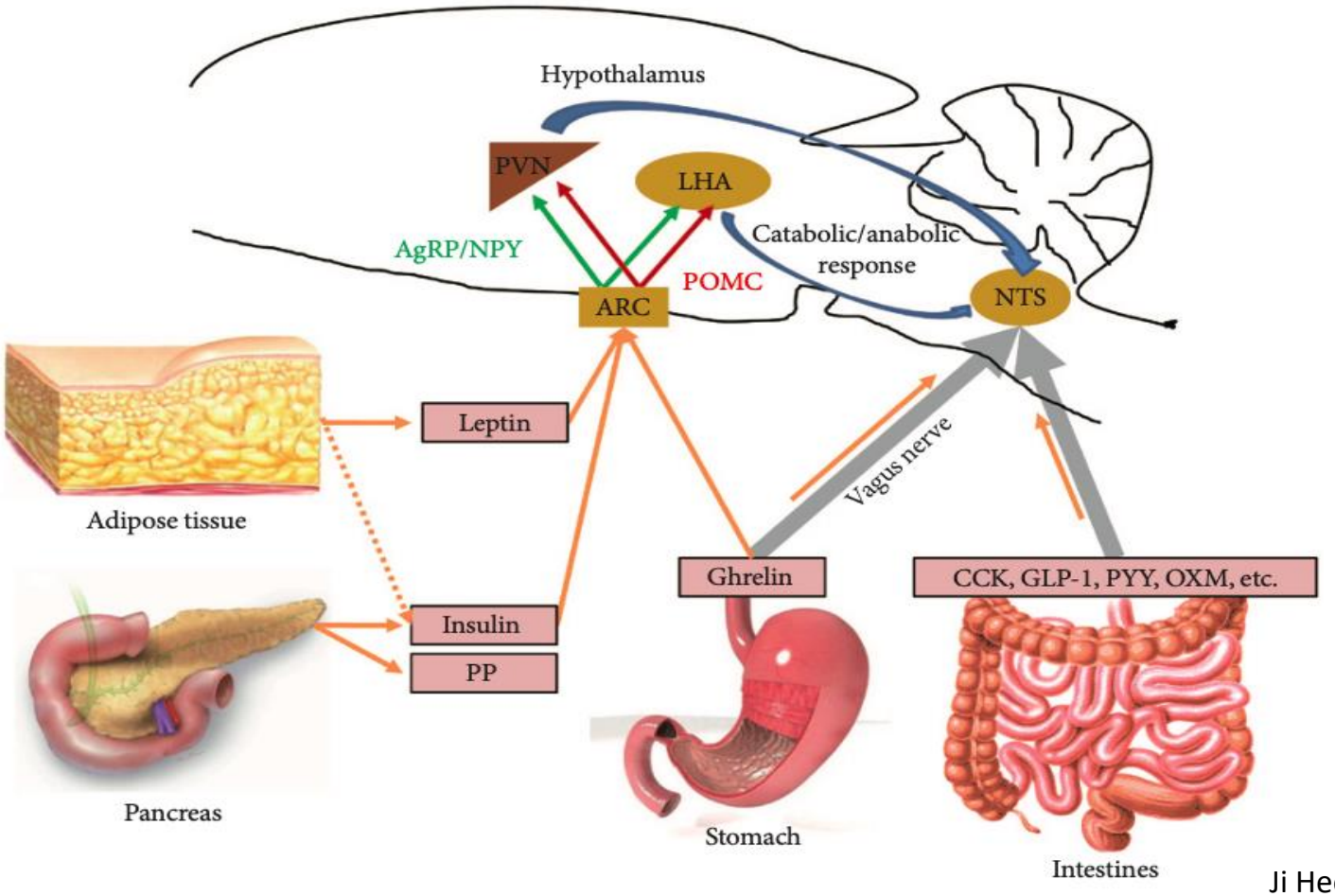
Su 20 persone intervistate con aumento di peso >20% solo 2 non erano soddisfatte
Nessuno ha richiesto sospensione o variazione della ART per variazione di peso

Presented at IAS 2019,
slides MOAX0102LB

La patogenesi ….



Inhibition of α-melanocyte stimulating hormone



A schematic representation of the multiple systems regulating appetite. AgRP, agouti-related peptide; ARC, arcuate nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; LHA, lateral hypothalamic area; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, peptide YY.

Ji Hee Yu et al. Diabetes Metab J 2012;36:391-398

Inhibition of α-melanocyte stimulating hormone

- In vitro studies demonstrated that dolutegravir inhibited the binding of radiolabelled α-melanocyte stimulating hormone to the human recombinant melanocortin 4 receptor, which may interfere with the regulation of food intake and lead to obesity

However, McMahon et al. subsequently found that drug concentrations substantially greater than clinical exposure are required for antagonism of the melanocortin-4 receptor to occur, thus refuting this hypothesis

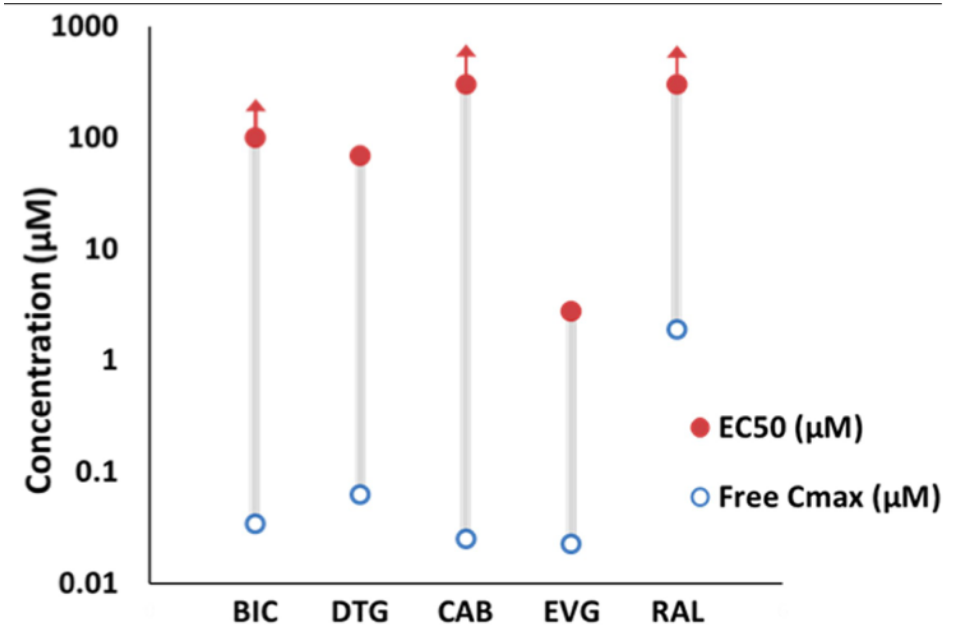


Fig 1. Depiction of MC4R antagonism assay results and clinical C_{max} margins for INSTIs. Lines depict the substantial difference between the clinical dose C_{max} value (protein-free) and the reported EC_{50} value in the MC4R antagonism assay for each INSTI evaluated.

Committee for Medicinal Products for Human Use (CHMP). European medicines agency. Assessment report. Dolutegravir (Tivicay). November 21, 2013; McMahon C et al. PLoS ONE. 2020;15:e0229617.

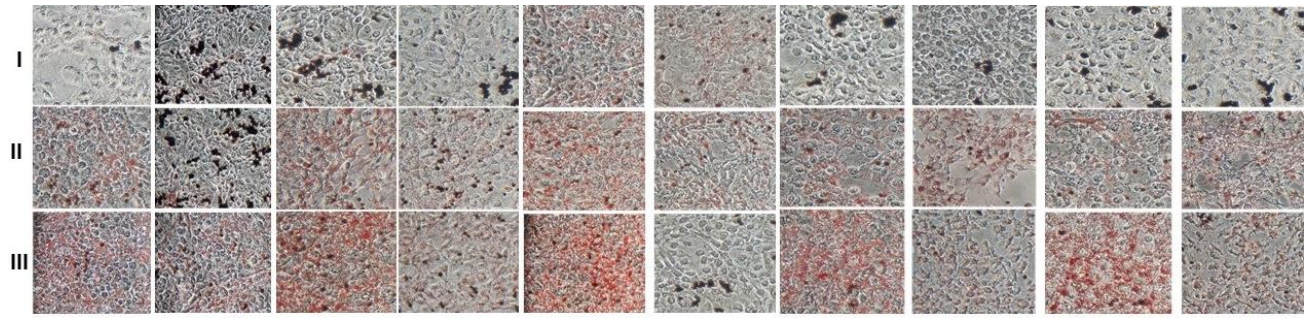
Adipocyte differentiation of 3T3-L1 cells under TAF, TDF and INSTIs selective challenge: an in vitro mode

AIDS. 2023 Mar 15;37(4):561-570.

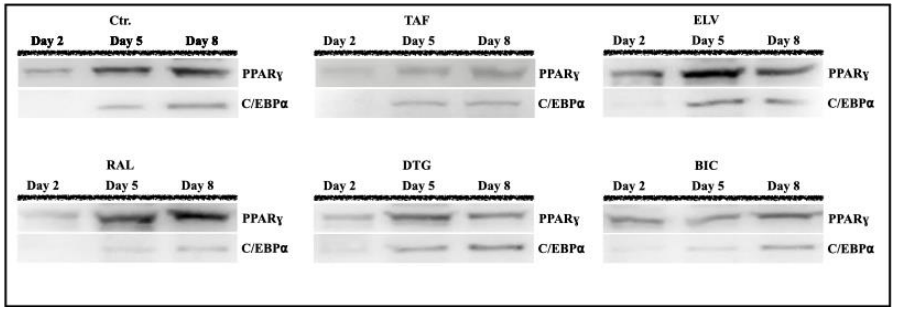
- Perna A, Carleo MA, Mascolo S, Guida A, Contieri M, Sellitto C, Hay E, de Blasiis P, Lucariello A, Guerra G, Baldi A, De Luca A, **Maggi P**, Esposito V.

BACKGROUND

The Integrase Strand Transfer Inhibitors (INSTI) class of drugs is characterized by a good tolerability profile and a relatively high genetic barrier to HIV drug resistance. However, several studies reported greater weight gain among persons receiving INSTI-based regimens for initial therapy as compared to protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens. These studies could be affected by several potential biases, because of the large number of metabolic comorbidities affecting these patients together to high risk of pharmacological interactions. Since adipocyte differentiation recognizes an important regulatory checkpoint by two families of transcription factors, the CCAAT/enhancer-binding proteins (C/EBPs) and the peroxisome proliferator-activated receptors (PPARs), the evaluation of the expression of adipocyte differentiation markers, such as PPAR-γ and C/EBP-α, is routinely used to evaluate fat tissue differentiation and it has been already assessed to investigate adipocyte differentiation in studies on HIV infected patients.



3T3L1 Red oil staining according to different steps of adipocyte differentiation and different antiretroviral drugs.



METHODS

We used the 3T3-L1 cells *in vitro* model of adipogenesis to investigate the effects on adipocyte differentiation of the newer NRTI, tenofovir alafenamide fumarate (TAF), alone or in combination with the four INSTIs, raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC). The effects of the drugs on cell viability were determined by the MTT assay (data not shown). Expression levels of PPARɣ and C/EBPα, and the intracellular lipid accumulation by Red Oil staining, were used to monitor adipocyte differentiation.

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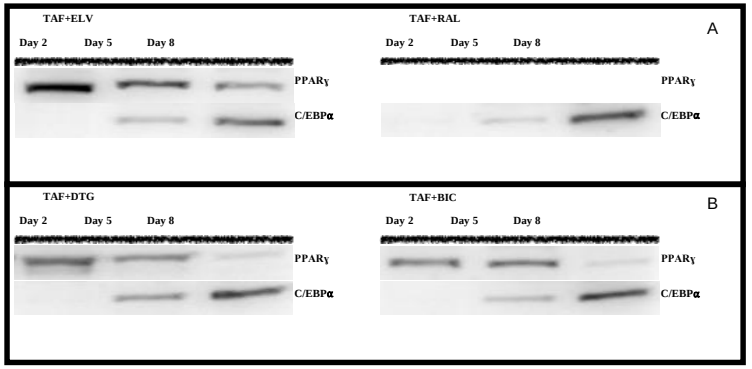
RESULTS

Compared to the control, RAL, EVG, DTG and BIC were all able to increase adipogenesis, being RAL and ELV somehow more efficient, while TAF slightly inhibited adipogenesis. When used in combination with the other INSTIs, TAF was able to reduce the adipogenic effects of all the four drugs. This effect was more evident when TAF was used in combination with DTG and BIC.

	Day 2 (PPAR)	Day 5 (PPAR)	Day 8 (PPAR)		Day 2 (C/EBP)	Day 5 (C/EBP)	Day 8 (C/EBP)
Cont.	1	2	3	Cont.	1	2	2 // 3
TAF	0-1	2	2	TAF	0-1	2	2
ELV	2	3	2	ELV	0	2	2
ELV+TAF	3	2	1	ELV+TAF	0	1	2
RAL	1	3	3	RAL	0	1	1
RAL+TAF	3	2	2	RAL+TAF	0	1	2
DTG	1	2	2	DTG	0-1	2	2
DTG+TAF	3	2	0 // 1	DTG+TAF	0	1	2
BIC	2	2	3	BIC	0-1	1	2
BIC+TAF	2	2	0 // 1	BIC+TAF	0	1	2



CONCLUSIONS

Several clinical data suggest that therapy with INSTIs could determine weight gain, especially if associated with TAF. Our results confirm that INSTIs could increase adipogenesis, while, on the other hand, in our 3T3L1 cells *in vitro* model of adipogenesis, TAF shows an inhibitory effect, being able to effectively contrast the increased adipogenesis caused by other INSTIs, in particular DTG and BIC. Taken together, these evidences are suggestive for an antagonistic effect of different antiretroviral drugs routinely used in therapeutic association on adipocyte differentiation. In the light of our observations we hypothesize that clinical data showing an additive effect of INSTIs and TAF on weight gain could be affected by biases due to the multifactorial nature of the weight gain phenomenon.

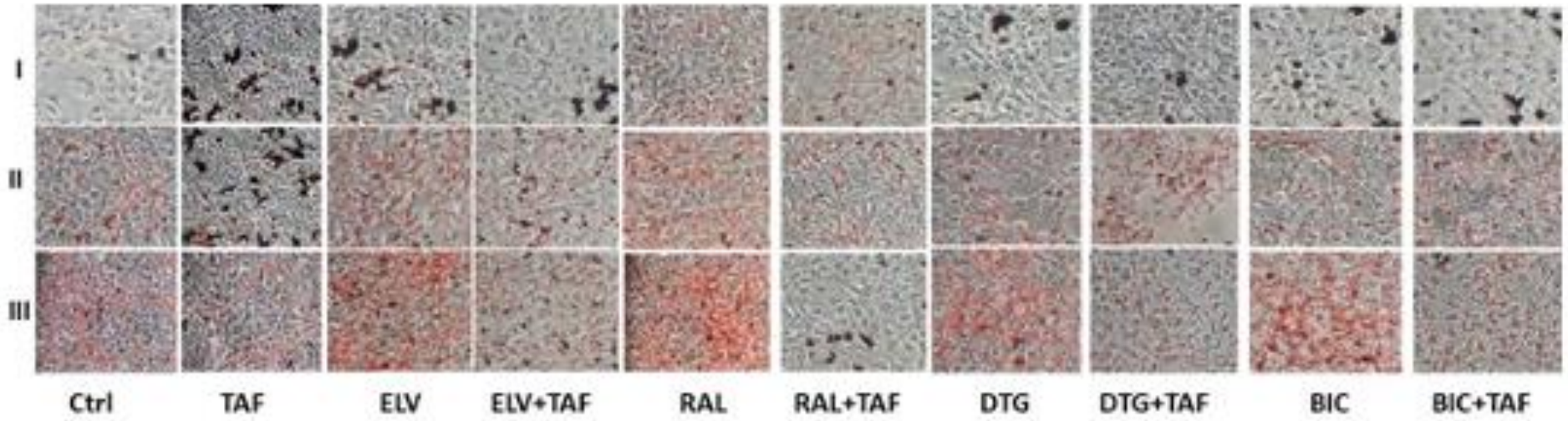
CROI 2022

00599

ADIPOCYTE DIFFERENTIATION AND ANTIRETROVIRAL DRUGS: AN IN VITRO MODEL

M. A. Carleo[1], A. Perna[2], P. Rosario[1], S. Mascolo[1], A. Lucariello[3], G. Palmiero[1], V. Rizzo[1], A. M. Rossomando[1], A. Baldi[4], A. De Luca[5], P. Maggi[6], **V. Esposito[1]**

[1]Infectious Diseases and Gender Medicine Unit "D. Cotugno" Hospital – AO dei Colli, Naples Italy, [2]Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy, [3]Department of Sport Sciences and Wellness, University of Naples "Parthenope", Naples, Italy, [4]Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, Università degli Studi della Campania "L. Vanvitelli", Caserta, Italy, [5]Department of Mental and Physical Health and Preventive Medicine, Section of Human Anatomy, University of Campania "Luigi Vanvitelli", Naples, Italy, [6]University of Campania "Luigi Vanvitelli", Caserta Italy.



3T3L1 Red oil staining according to different steps of adipocyte differentiation and different antiretroviral drugs.

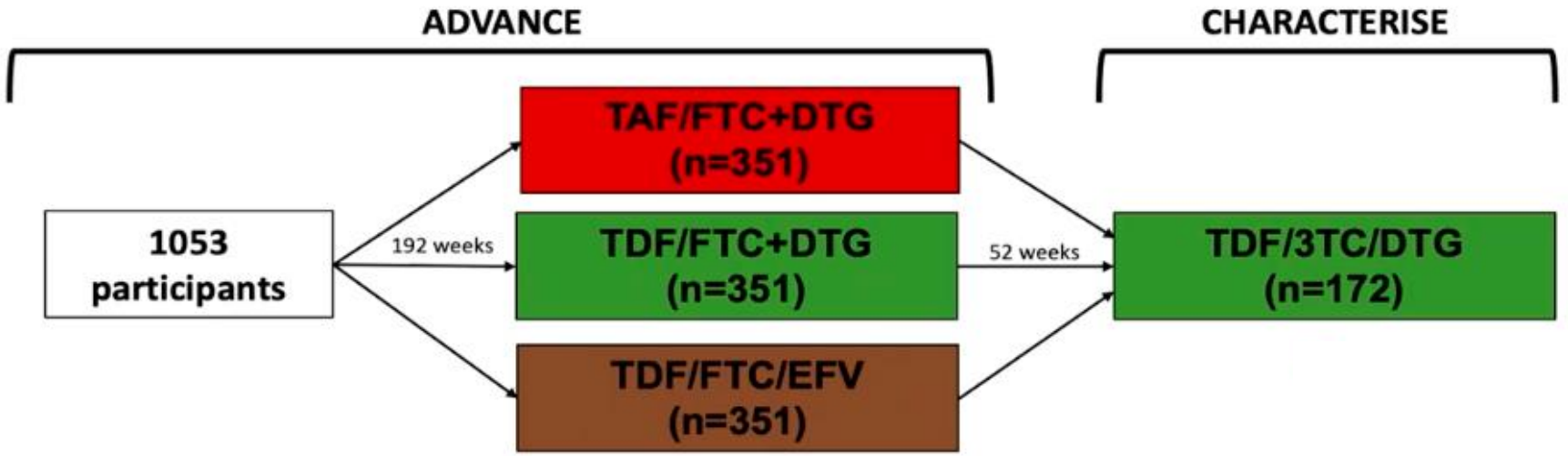
RESULTS

Compared to the control, RAL, EVG, DTG and BIC were all able to increase adipogenesis, being RAL and ELV somehow more efficient, while TAF slightly inhibited adipogenesis. When used in combination with the other INSTIs, TAF was able to reduce the adipogenic effects of all the four drugs. This effect was more evident when TAF was used in combination with DTG and BIC.

CONCLUSIONS

Several clinical data suggest that therapy with INSTIs could determine weight gain, especially if associated with TAF. Our results confirm that INSTIs could increase adipogenesis, while, on the other hand, in our 3T3L1 cells *in vitro* model of adipogenesis, TAF shows an inhibitory effect, being able to effectively contrast the increased adipogenesis caused by other INSTIs, in particular DTG and BIC. Taken together, these evidences are suggestive for an antagonistic effect of different antiretroviral drugs routinely used in therapeutic association on adipocyte differentiation. In the light of our observations we hypothesize that clinical data showing an additive effect of INSTIs and TAF on weight gain could be affected by biases due to the multifactorial nature of the weight gain phenomenon.

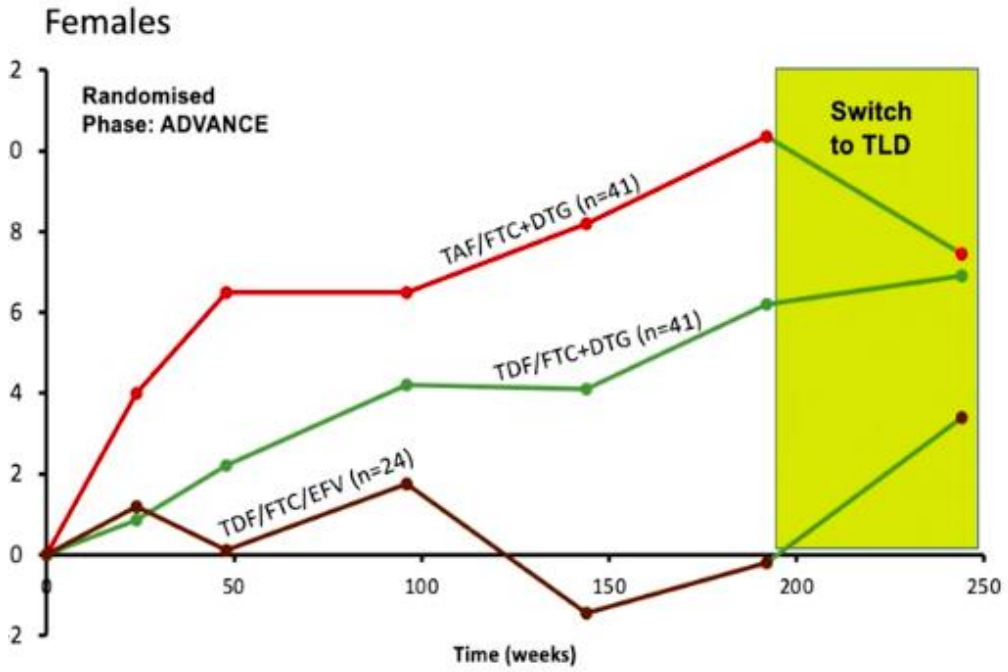
ADVANCE and CHARACTERISE trials

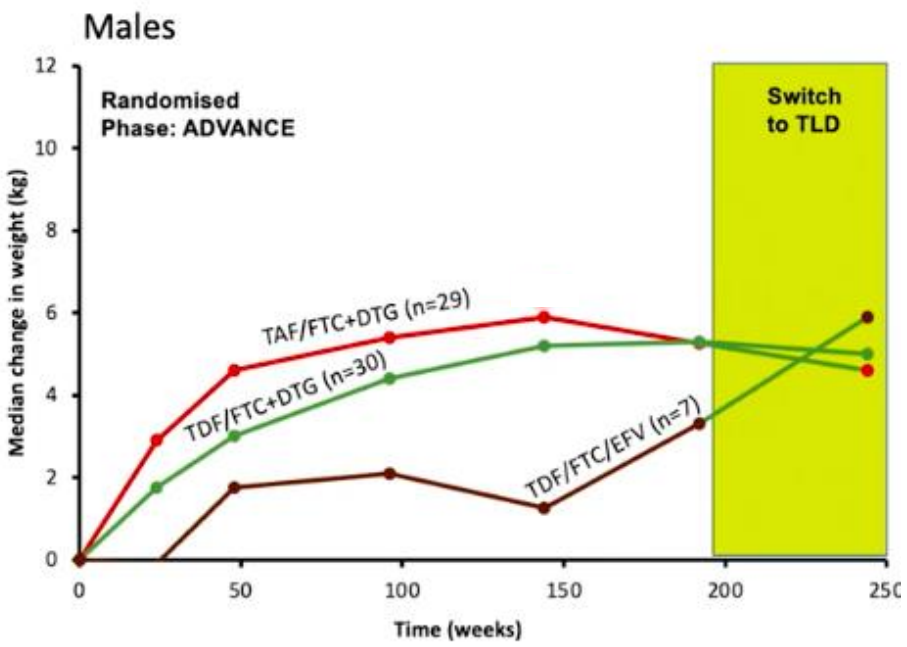


- At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA

- Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TDF/3TC/DTG were evaluated in each treatment arm using paired non-parametric tests

Change in weight after switch to TDF/3TC/DTG – Females and Males





REVERSIBILITY OF TAF- AND/OR INSTI-ASSOCIATED WEIGHT GAIN
Athena Cohort

- Assess the reversibility of ≥7% TAF- and/or INSTI-associated weight gain (WG) in virally suppressed ART-experienced people with HIV (PWH) from the Dutch ATHENA cohort [1]

- Included: PWH with ≥7% WG within 24 months after a first switch to a regimen containing only TAF, only an INSTI or both TAF+INSTI
- Excluded: hypothyroidism, Cushing's syndrome, congestive heart failure, renal failure, liver cirrhosis, use of corticosteroids, antidepressants or antipsychotics

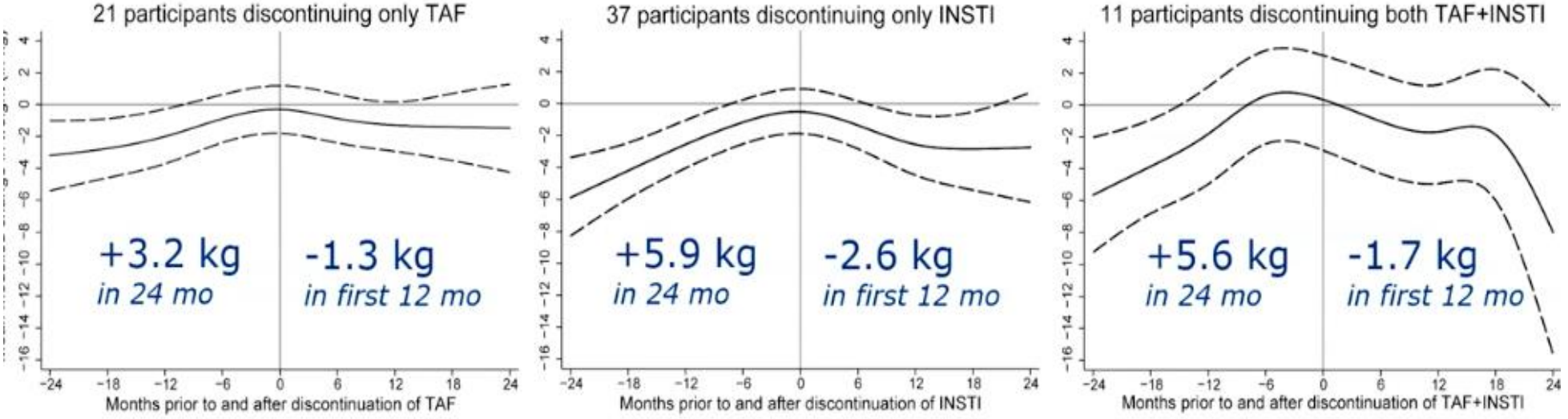
1440 of 6245 eligibe participants gained >=7% weight gain after switch to TAF and/or INSTI

Included in analysis:
Discontinuation of TAF and/or INSTI after first recording of ≥7% weight gain (n = 69)

- 21 discontinuing only TAF
- 37 discontinuing only INSTI
- 11 discontinuing both TAF+INSTI

Myrthe L. Verburgh et al., CROI 2023 **ABSTRACT 673**

Adjusted mean modelled weight change prior/after discontinuation



Factors associated with weight change after discontinuation

- BMI ≥30kg/m^2 at discontinuation associated with greater weight loss
  - -5.4 kg/yr more [95%CI, -9.2 to -1.7] vs in individuals with BMI 18.5-24.9kg/m^2
- No independent associations between changes in NRTI backbone or anchor agent at moment of discontinuation and subsequent weight change

Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain

Kai Juhani Kauppinen[a,b], Inka Aho[a,b] and Jussi Sutinen[a,b]

Table 4. Body weight at baseline (BL), follow-up 1 (FU-1), and follow-up 2 (FU-2).

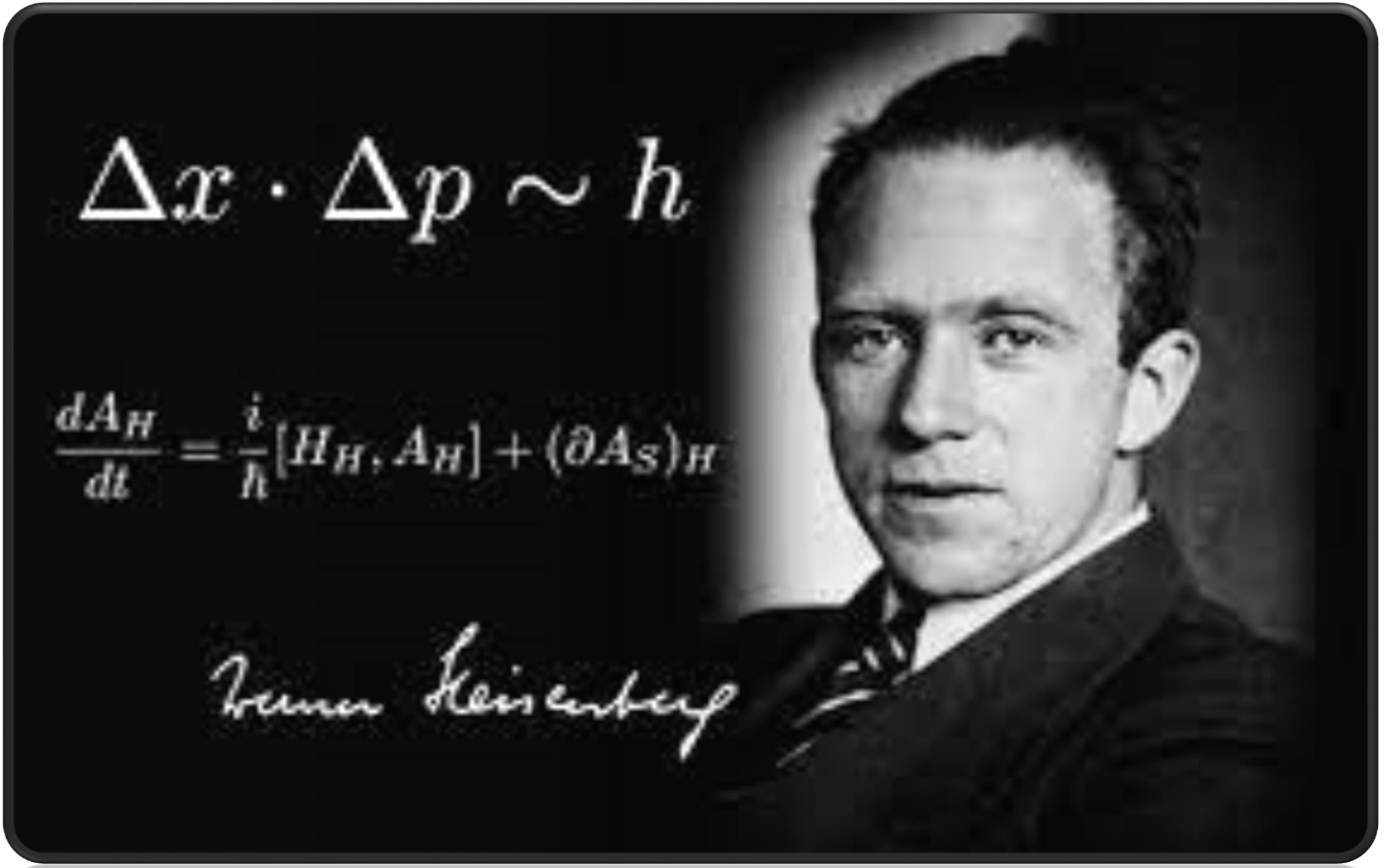
	Weight (kg) at BL	Weight (kg) at FU-1	Weight (kg) at FU-2	*P* value*
Switch group	80.8 (15.5), $n=65$[a]	80.8 (17.7), $n=65$	NA	0.293
Control group	81.9 (17.4), $n=90$[a]	82.8 (17.8), $n=90$	NA	**0.001**
Switch group	83.1 (18.9), $n=95$[b]	NA	83.7 (20.3), $n=95$	0.978
Control group	83.4 (17.6), $n=110$[b]	NA	84.9 (18.6), $n=110$	**0.025**

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. Data are given as mean (standard deviation).

*P-value for the pairwise comparison between BL and FU-1/FU-2 within the study group.

[a]P-value for the comparison between Switch and Control group at Baseline: P = 0.686

Il principio di indeterminazione di Eisemberg



Ma l'obesità è davvero un fattore di rischio?

↑ DTG + TAF/FTC vs EFV/TDF/FTC	**ADVANCE:** QRISK score in ART-naïve participants (N=1,053), randomised to DTG + TAF/FTC, DTG + TDF/FTC or EFV/TDF/FTC[1]
↑ INIs vs non-INI (short term) = (long term)	**RESPOND:** Incidence of CVD in INI-naïve patients exposed to DTG, EVG/c or RAL during follow-up (N=29,340)[2]
= BIC/TAF/FTC vs DTG	**Rolle et al:** Switch to BIC/TAF/FTC (N=673) versus various DTG-based regimens (N=283); no significant changes in cardiometabolic parameters between treatment groups at Week 48[3]
= DTG/3TC vs TAF-based regimens	**TANGO:** Adjusted odds of Framingham risk score ≥10% were similar between DTG/3TC and TAF-based regimen groups (N=741)[4]
= INIs vs non-INI	**Swiss HIV Cohort Study:** Over a median of 4.9 years' follow-up, no difference was observed in CV events between treatment-naïve patients starting INIs and those starting other ART (N=5,362)[5]

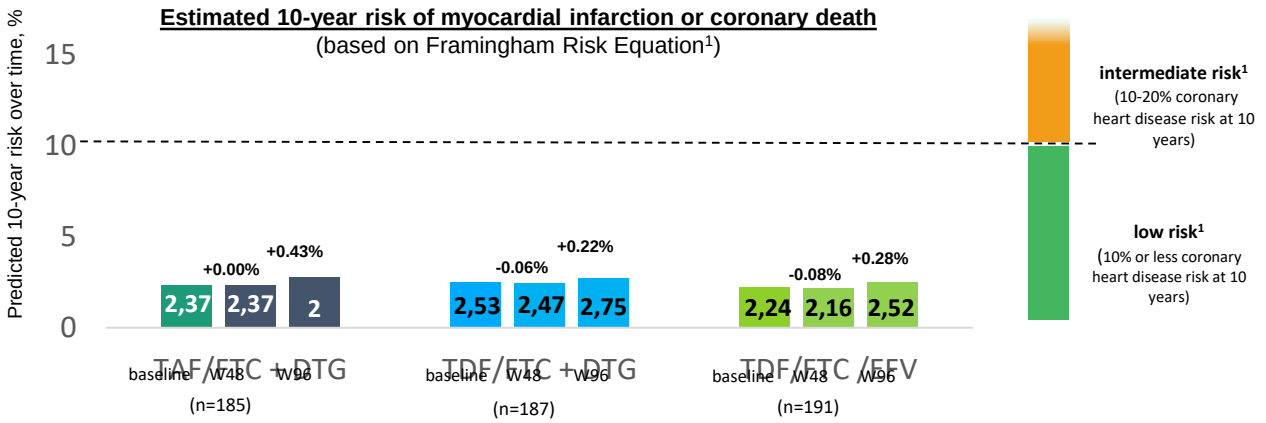
Current data linking **CVD risk** and INIs are limited and inconclusive; further longer-term studies are required[1–5]

Key – overall study results show:

↑ **Increased risk** = **No association** ↓ **Decreased risk**

1. McCann K, et al. AIDS 2021;35:1657–65;
2. Neesgaard B, et al. Lancet HIV 2022;9:e474–85; **3.** Rolle CP, et al. AIDS 2022. Poster EPB116
4. Batterham RL, et al. Int Workshop Long-term Complications HIV SARS-CoV-2 2021. Slides ADRLH 25
5. Surial B, et al. CROI 2023. Oral 149

Framingham Cardiovascular Events Prediction



No difference in Framingham risk equation results at W96 among the three arms*

* no p value was reported

Adapted from Hill A, et al. CROI 2020. Boston, MA. Oral 81

1. Framingham Heart Study Project, accessible on https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

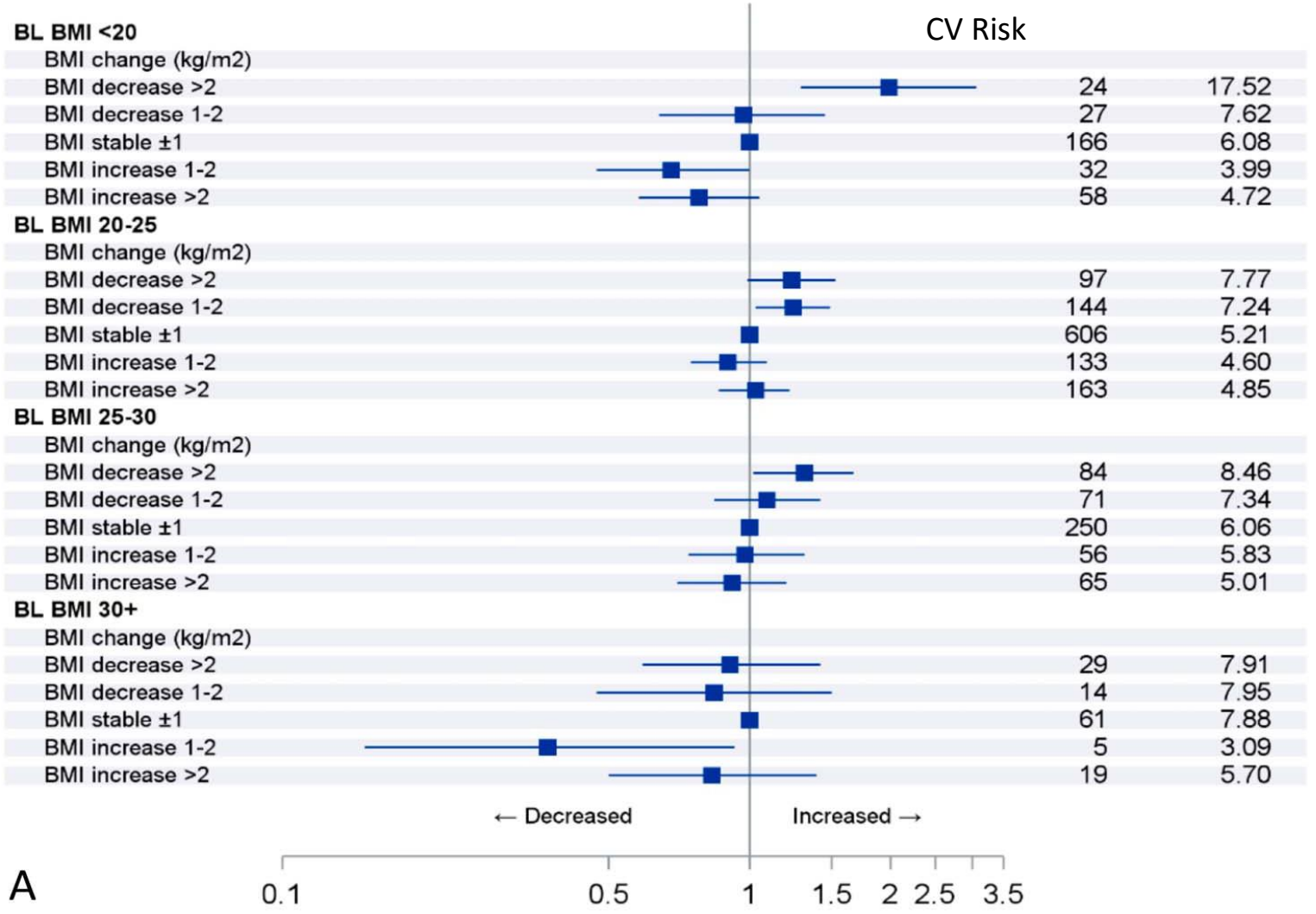
J Acquir Immune Defic Syndr • Volume 86, Number 5, April 15, 2021

CLINICAL SCIENCE

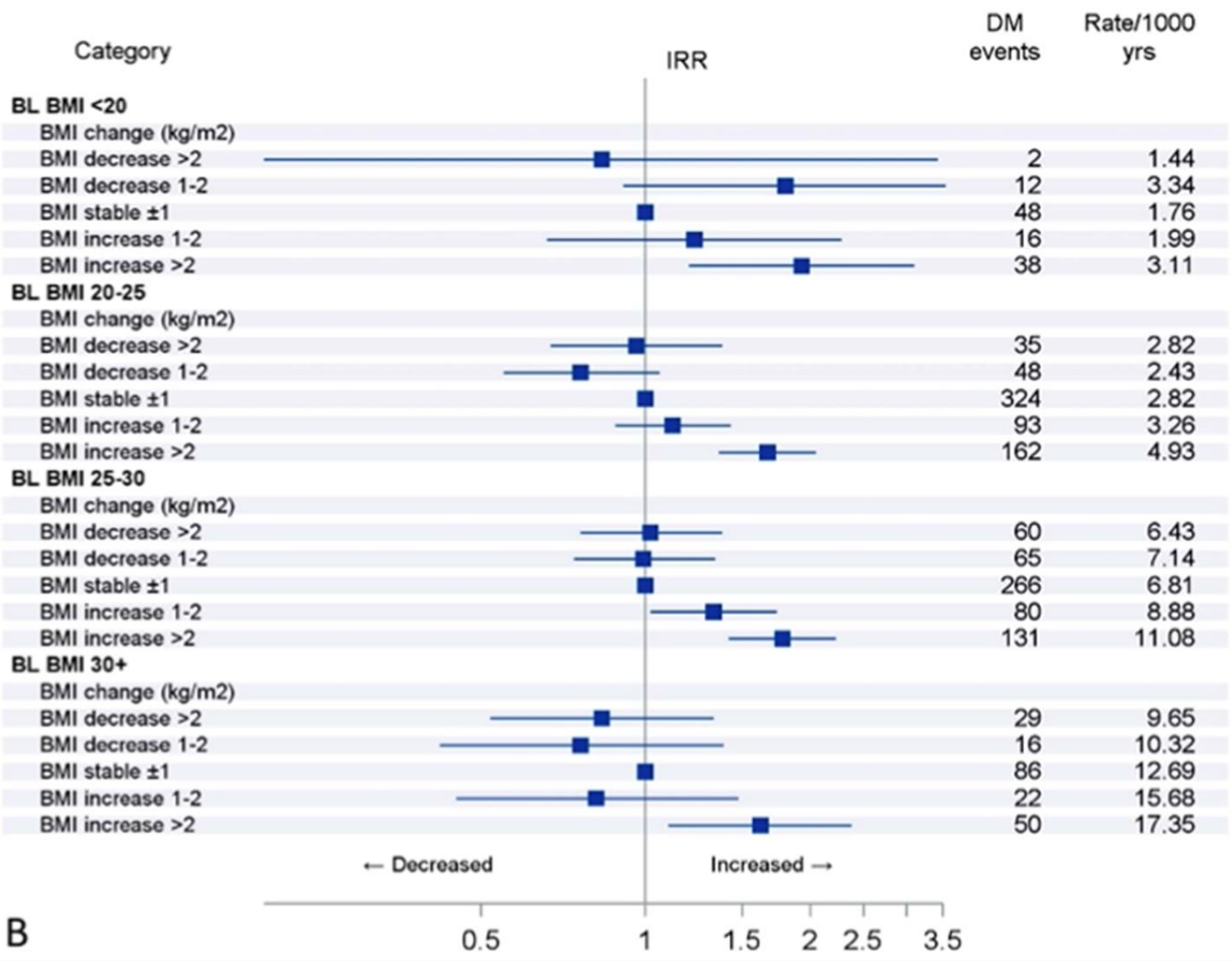
Effect of Changes in Body Mass Index on the Risk of Cardiovascular Disease and Diabetes Mellitus in HIV-Positive Individuals: Results From the D:A:D Study

Kathy Petoumenos, PhD,[a] Locadiah Kuwanda, MMed Statistics,[a] Lene Ryom, MD, PhD,[b] Amanda Mocroft, PhD,[c] Peter Reiss, MD, PhD,[d,e] Stephane De Wit, MD,[f] Christian Pradier, MD,[g] Fabrice Bonnet, MD, PhD,[h] Andrew Phillips, PhD,[c] Camilla I. Hatleberg, MD, PhD,[b] Antonella d'Arminio Monforte, MD, PhD,[i] Rainer Weber, MD, DTM&H,[j] Caroline A. Sabin, PhD,[c] Jens Lundgren, MD, DMSc, PhD,[b] and Matthew G. Law, PhD,[a] for the D:A:D Study Group

SOLO NAIVE	NAIVE e EXPERIENCED
9,321 pazienti inclusi	43,805 pazienti inclusi
43,982 PYFU	365,287 PYFU


CV Risk
BL BMI <20
BMI change (kg/m2)
BMI decrease >2 24 17.52
BMI decrease 1-2 27 7.62
BMI stable ±1 166 6.08
BMI increase 1-2 32 3.99
BMI increase >2 58 4.72
BL BMI 20-25
BMI change (kg/m2)
BMI decrease >2 97 7.77
BMI decrease 1-2 144 7.24
BMI stable ±1 606 5.21
BMI increase 1-2 133 4.60
BMI increase >2 163 4.85
BL BMI 25-30
BMI change (kg/m2)
BMI decrease >2 84 8.46
BMI decrease 1-2 71 7.34
BMI stable ±1 250 6.06
BMI increase 1-2 56 5.83
BMI increase >2 65 5.01
BL BMI 30+
BMI change (kg/m2)
BMI decrease >2 29 7.91
BMI decrease 1-2 14 7.95
BMI stable ±1 61 7.88
BMI increase 1-2 5 3.09
BMI increase >2 19 5.70
← Decreased
Increased →
0.1
0.5
1
1.5
2
2.5
3.5

A


Category
IRR
DM events
Rate/1000 yrs
BL BMI <20
BMI change (kg/m2)
BMI decrease >2 2 1.44
BMI decrease 1-2 12 3.34
BMI stable ±1 48 1.76
BMI increase 1-2 16 1.99
BMI increase >2 38 3.11
BL BMI 20-25
BMI change (kg/m2)
BMI decrease >2 35 2.82
BMI decrease 1-2 48 2.43
BMI stable ±1 324 2.82
BMI increase 1-2 93 3.26
BMI increase >2 162 4.93
BL BMI 25-30
BMI change (kg/m2)
BMI decrease >2 60 6.43
BMI decrease 1-2 65 7.14
BMI stable ±1 266 6.81
BMI increase 1-2 80 8.88
BMI increase >2 131 11.08
BL BMI 30+
BMI change (kg/m2)
BMI decrease >2 29 9.65
BMI decrease 1-2 16 10.32
BMI stable ±1 86 12.69
BMI increase 1-2 22 15.68
BMI increase >2 50 17.35
← Decreased
Increased →
0.5
1
1.5
2
2.5
3.5

B

Change in body mass index (BMI) and association with clinical outcomes after initiation of contemporary HIV antiretroviral (ARV) regimens in EuroSIDA

EACS 2021 Oct 27-30 London, UK

Wendy Bannister1, T. Christopher Mast2, Lars Peters1, Stéphane De Wit3, Jan Gerstoft4, Lothar Wiese5, Ana Milinkovic6, Vesna Hadziosmanovic7, Margaret Johnson8, Amanda Mocroft1,9, Amanda Clarke10, Karine Lacombe11, Philipp Schommers12, Therese Staub13, Alexandra Zagalo14, Jose Joaquin Portu15, Luba Tau16, Alexandra Calmy17, Matthias Cavassini18, Martin Gisinger19, Elena Borodulina20, and Joanne Reekie1, for the EuroSIDA study group.

EuroSIDA

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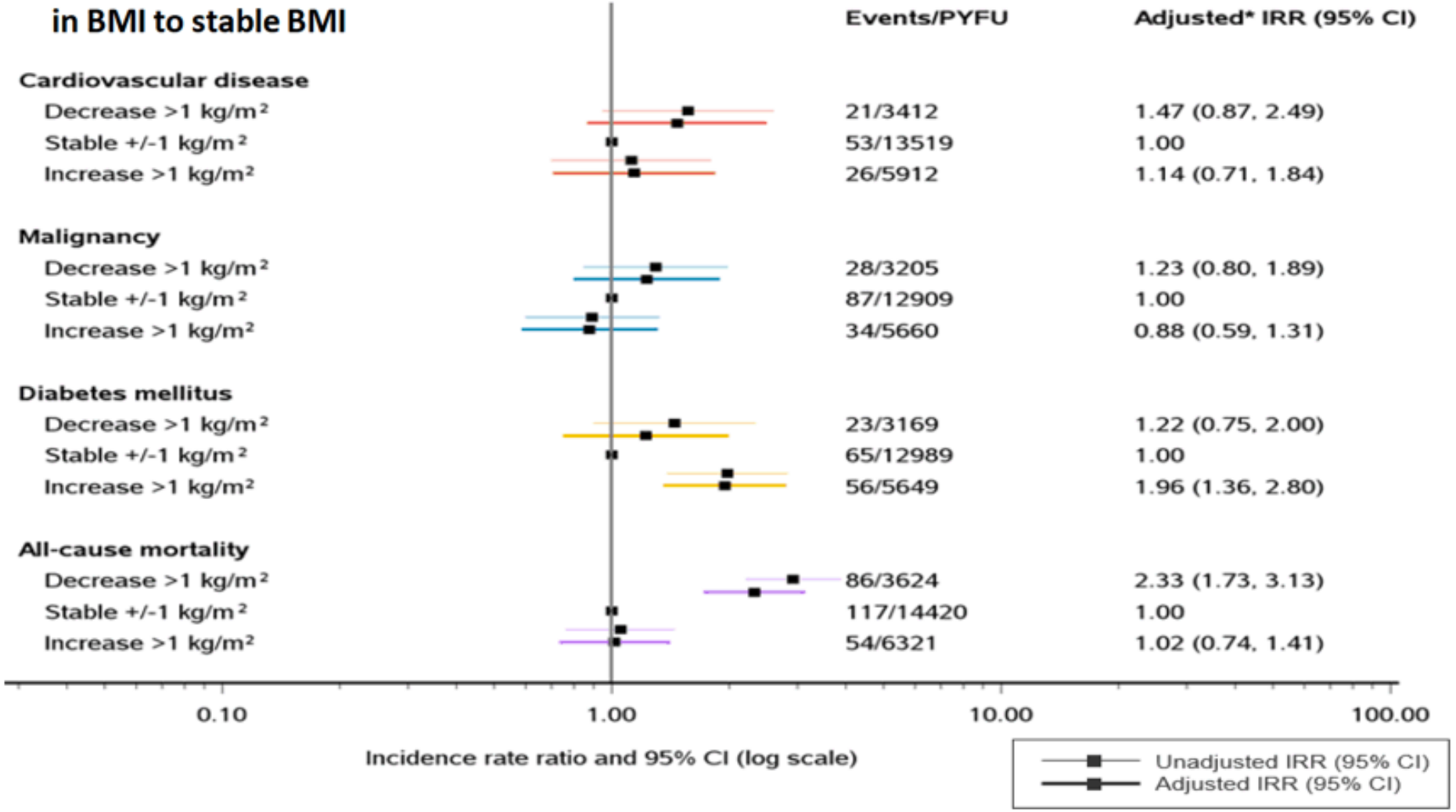
chip
Centre of Excellence for
Health, Immunity and Infections

Figure 2 Incidence rate ratios (IRRs) and 95% CIs comparing changes from baseline in BMI to stable BMI



viruses

MDPI

Article

Lipids and Transaminase in Antiretroviral-Treatment-Experienced People Living with HIV, Switching to a Doravirine-Based vs. a Rilpivirine-Based Regimen: Data from a Real-Life Setting

Paolo Maggi [1], Elena Delfina Ricci [2,*], Canio Vito Martinelli [3], Giuseppe Vittorio De Socio [4], Nicola Squillace [5], Chiara Molteni [6], Addolorata Masiello [1], Giancarlo Orofino [7], Barbara Menzaghi [8], Rita Bellagamba [9], Francesca Vichi [10], Benedetto Maurizio Celesia [11], Giordano Madeddu [12], Giovanni Francesco Pellicanò [13], Maria Aurora Carleo [14], Antonio Cascio [15], Andrea Parisini [16], Lucia Taramasso [17], Laura Valsecchi [18], Leonardo Calza [19], Stefano Rusconi [20], Eleonora Sarchi [21], Salvatore Martini [22], Olivia Bargiacchi [23], Katia Falasca [24], Giovanni Cenderello [25], Sergio Ferrara [26], Antonio Di Biagio [17] and Paolo Bonfanti [5,27,†] on behalf of the CISAI Study Group

Viruses **2023**, *15*, 1612. https://doi.org/10.3390/v15071612 https://www.mdpi.com/journal/viruses

Table 2. Change from baseline to T1 (mean, 95% confidence interval) comparison between DOR-based and RPV-based regimens.

T1-T0	Doravirine N=256	Rilpivirine N=295	P*
BMI, Kg/m^2	-0.1 (-0.3, 0.1)	**0.1 (0.0, 0.2)**	0.18
Weight, Kg	-0.1 (-0.6, 0.4)	**0.3 (0.0, 0.6)**	0.24
Total cholesterol, mg/dL	**-20 (-24, -15)**	**-16 (-20, -12)**	0.89
HDL-cholesterol, mg/dL	-1 (-2, 0)	-3 (-4, -2)	0.09
Total cholesterol /HDL-cholesterol	**-0.36 (-0.48, -0.23)**	-0.08 (-0.25, 0.08)	0.39
LDL-cholesterol, mg/dL	-14 (-19, -10)	-9 (-13, -6)	0.26
Triglycerides, mg/dL	-22 (-34, -9)	-22 (-33, -11)	0.12
Not on lipid-lowering drugs			
Total cholesterol, mg/dL	-19 (-23, -14)	-17 (-21, -13)	0.34
HDL-cholesterol, mg/dL	-1 (-2, 1)	**-3 (-4, -2)**	0.0005
Total cholesterol /HDL-cholesterol	**-0.33 (-0.45, -0.22)**	-0.05 (-0.22, 0.13)	0.24
LDL-cholesterol, mg/dL	-14 (-19, -10)	-10 (-13, -6)	0.43
Triglycerides, mg/dL	-21 (-35, -6)	-20 (-32, -8)	0.14
Liver enzymes			**P****
AST ≤40 UI/L at T0	**2 (1, 3)**	**3 (2, 4)**	0.02
AST >40 UI/L at T0	-6 (-21, 7)	-1 (-11, 9)	0.44
ALT ≤40 UI/L at T0	**3 (2, 5)**	**8 (6, 11)**	0.0001
ALT >40 UI/L at T0	**-14 (-24, -4)**	-2 (-12, 8)	0.45

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DOR1: lamivudine/tenofovir disoproxil fumarate; DOR2: other DOR-based regimens; HDL: high density lipoprotein; LDL: low density lipoprotein

Bold: change from baseline $p<0.05$ (paired t-test).

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BMC Infectious Diseases

RESEARCH Open Access

Lipids and transaminase elevations in ARV-experienced PLWH switching to a doravirine-based regimen from rilpivirine or other regimens

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Table 1 Baseline values and 6-month follow-up modifications (DOR1: on doravirine switched from rilpivirine-based regimens; DOR2: on doravirine, switching from other NNRTI-containing regimens, DOR3: on doravirine, switching from INSTI-containing regimens)

Variable	DOR1 n = 35	DOR2 n = 32	DOR3 n = 40	P*
Current regimen, n (%)	31 (88.6%)	17 (53.1%)	22 (55.0%)	0.006
3TC/TDF/DOR	3 (8.6%)	7 (21.9%)	12 (30.0%)	
Dual with INSTI	1 (2.9%)	8 (25.0%)	6 (15.0%)	
FTC/TAF/DOR				
TAF in the previous regimen, n (%)	5 (14.3%)	6 (18.8%)	26 (65.0%)	< 0.0001
Blood lipids				
Total cholesterol, mg/dL				
Baseline, mean ± SD	181 ± 40	203 ± 44	199 ± 46	0.079
T1-T0, mean (95% CI)	*-6 (-18, +6)*	***-15 (-26, -5)***	***-23 (-32, -13)***	*0.053*
HDL-cholesterol, mg/dL				
Baseline, mean ± SD	46 ± 13	55 ± 14	49 ± 16	0.020
T1-T0, mean (95% CI)	*3 (-1, +8)*	*-2 (-6, +2)*	*-0 (-3, +3)*	*0.059*
Total cholesterol /HDL-cholesterol				
Baseline, median (IQR)	4.0 (3.6–4.7)	3.6 (3.1–4.5)	4.1 (3.4–4.9)	0.339
T1-T0, mean (95% CI)	*-0.23 (-0.61, + 0.14)*	*-0.19 (-0.54, +0.16)*	***-0.45 (-0.75, -0.15)***	*0.435*
LDL-cholesterol, mg/dL				
Baseline, mean ± SD	110 ± 34	119 ± 37	120 ± 42	0.530
T1-T0, mean (95% CI)	*-8 (-18, +3)*	***-12 (-22, -3)***	***-22 (-31, -14)***	*0.055*
Triglycerides, mg/dL				
Baseline, median (IQR)	121 (75–145)	107 (89–152)	120 (99–200)	0.156
T1-T0, mean (95% CI)	*-9 (-38, +18)*	*-19 (-43, +6)*	*-8 (-30, +14)*	*0.791*
Liver enzymes				
ALT ≤ 40 UI/L at T0, n (%)	29 (82.9%)	27 (84.4%)	30 (75.0%)	0.550
Baseline, median (IQR)	21 (19–27)	19 (14–26)	19 (15–26)	0.586
T1-T0, mean (95% CI)	*-2 (-7, +2)*	*1 (-3, +6)*	*2 (-1, +6)*	*0.211*
ALT > 40 UI/L at T0, n (%)	6 (17.1%)	5 (15.6%)	10 (25.0%)	0.550
Baseline, median (IQR)	50 (45–63)	49 (42–74)	80 (51–91)	0.260
T1-T0, mean (95% CI)	*-18 (-44, +7)*	*10 (-16, +37)*	***-26 (-42, -9)***	*0.084*

3TC: lamivudine; ALT: alanine aminotransferase; CI: confidence interval; DOR: doravirine; FTC: emtricitabine; HDL: high density lipoprotein; INSTI: integrase strand inhibitor; IQR: interquartile range; LDL: low density lipoprotein; TAF: tenofovir alafenamide

Bold: change from baseline $p < 0.05$.

* chi-square test, Mann-Whitney test, or analysis of variance, as appropriate. Changes from baseline were compared among groups using a multivariable linear model including the age at study entry, the initial level of the variable, the current regimen, the concurrent use of lipid lowering drugs and TAF in the previous regimen.

Abstract

Background Doravirine (DOR) is a newly approved antiretroviral belonging to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), well tolerated and leading to an improved lipid profile in antiretroviral experienced people living with HIV (PLWH). We aimed at evaluating if the lipid-lowering effect is linked to the drug class, using real-life data from the SCOLTA cohort.

Methods We compared the lipid profile modifications in experienced PLWH switching to a DOR-based regimen from rilpivirine or another NNRTI-based regimen or from an integrase strand transferase (INSTI)-based regimen. T0 and T1 were defined as the baseline and 6-month follow-up respectively. Data were collected at baseline and prospectively every six months and changes from baseline were compared using a multivariable linear model.

Results In 107 PLWH, enrolled in the SCOLTA DOR cohort, with undetectable HIV-RNA at baseline, 32.7% switched from RPV-based regimens (DOR1), 29.9% from other NNRTI-including regimens (DOR2) and 37.4% switched from INSTI-including regimens (DOR3). At T1, TC significantly decreased in DOR2 (-15 mg/dL) and DOR3 (-23 mg/dL), and significantly more in DOR3 than in DOR1 (-6 mg/dL) ($p = 0.016$). HDL-C declined in DOR2 (-2 mg/dL) whereas it increased in DOR1 (+3 mg/dL) ($p = 0.042$) and remained stable in DOR3. LDL-C significantly decreased from baseline in DOR2 (-12 mg/dL) and DOR3 (-22 mg/dL) and was different between DOR1 (-8 mg/dL) and DOR3 ($p = 0.022$). TC/HDL ratio showed a significant decline in the DOR3 group (-0.45), although similar to DOR1 (-0.23, $p = 0.315$) and DOR2 (-0.19, $p = 0.254$). Triglycerides did not noticeably change. ALT significantly decreased in PLWH with a baseline level > 40 UI/mL.

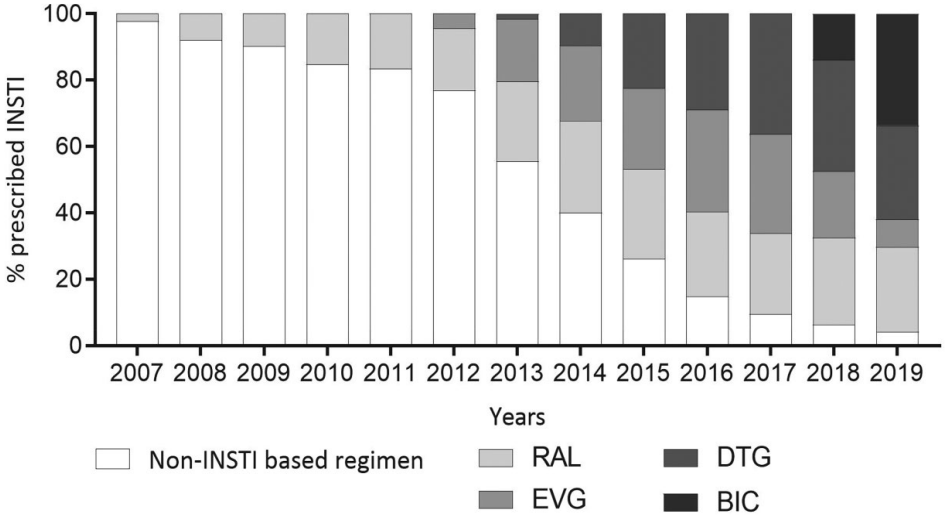
Conclusions PLWH on doravirine treatment showed different trends in blood lipids according to their previous regimen. In PLWH switching from RPV, minimal modifications were seen, whereas in those switching from other NNRTIs and from INSTI-including regimens, we observed an overall improvement in lipid profile, seemingly independent of the "statin effect" of TDF.

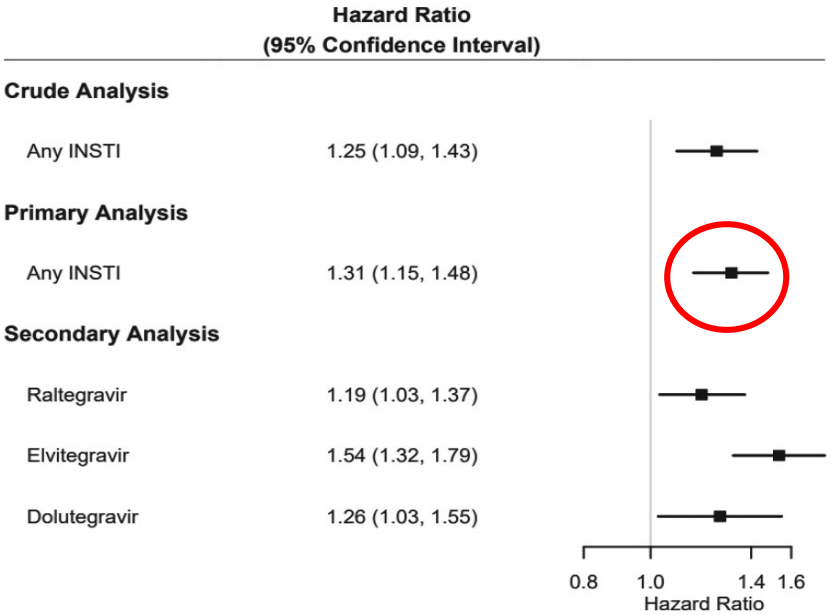
Keywords HIV infection, ART-experienced, Doravirine, Rilpivirine, Adverse events, Metabolic safety, Hepatic safety

Integrase Strand Transfer Inhibitors Are Associated With **Incident Diabetes Mellitus** in PWHIV

Results

- 42,382 PWH: **54% were treated with INSTI-based regimens**.
- Mean age **38 years**, 74% male.
- **PWH on INSTIs were 31% more likely to develop new-onset diabetes mellitus/hyperglycemia (HR 1.31)** compared to those who initiated non-INSTI based regimens.
- **The highest risk was associated with elvitegravir** (aHR 1.54) and the **lowest risk with raltegravir** (aHR 1.19).





➢ **INSTI use was associated with increased risk of new-onset diabetes mellitus/hyperglycemia in the six months following ART initiation.**

O'Halloran et al_Clin Infect Dis. 2022

BICTEGRAVIR and DOLUTEGRAVIR have no impact on glucose levels 12 months after initiation

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Table 2. Variation from T0 to T1 (BIC vs DTG)

	T1-T0		
Variables	Mean (95% CI)		
	BIC N=571	**DTG** N=1176	P
Weight, Kg	**0.9 (0.2, 1.6)**	**1.3 (1.0, 1.7)**	0.30
BMI, Kg/m^2	**0.2 (0.0, 0.5)**	**0.4 (0.3, 0.6)**	0.18
WC, cm (n=341/468)	1.5 (-0.7, 3.7)	**1.4 (0.6, 2.2)**	0.94
Total Cholesterol, mg/dL	-2 (-5, 1)	0 (-3, 3)	0.30
LDL-C, mg/dL	1 (-2, 4)	-1 (-3, 2)	0.48
HDL-C, mg/dL	**-2 (-3, -0)**	**2 (1, 3)**	<0.0001
TGL, mg/dL	-5 (-13, 2)	**-9 (-15, -3)**	0.46
BG, mg/dL	0 (-1, 2)	**1 (0, 2)**	0.56

Bold: p<0.05 for change from baseline. Legend to the table: BMI, Body Mass Index; WC, Waist circunfererence; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein, TGL , Triglycerides;BG, Blood Glucose.

in this cohort.

Table 3. Variation frm T0 to T1 (Experienced vs Naive)

	T0			T1-T0		
	Mean ± SD or median (IQR) or no (%)			Mean (95% CI)		
	E no=1705	N no=567	P	E diff N=1265	N diff N=378	P
Age, years	50.0 ± 11.6	41.8 ± 12.3	<0.0001	-	-	-
Weight, Kg	73.5 ± 14.3	70.0 ± 13.3	<0.0001	**0.6 (0.3, 1.0)**	**3.3 (2.6-4.0)**	<0.0001
BMI, Kg/m^2	25.1 ± 4.3	23.4 ± 3.8	<0.0001	**0.2 (0.1, 0.3)**	**1.1 (0.9, 1.3)**	<0.0001
WC, cm (n=618/191)	92.4 ± 114.4	87.0 ± 12.9	<0.0001	**1.2 (0.1, 2.3)**	**2.3 (0.9, 3.7)**	0.21
BG, mg/dL	91 ± 15	87 ± 14	<0.0001	1 (0, 2)	0 (-2, 1)	0.11

Legend to the table: Bold: p<0.05 for change from baseline ; BMI, Body Mass Index; WC, Waist Circumference; E, experienced to Antiretroviral Treatment; N, naïve to Antiretroviral Treatment; BG, Blood Glucose

Conclusions

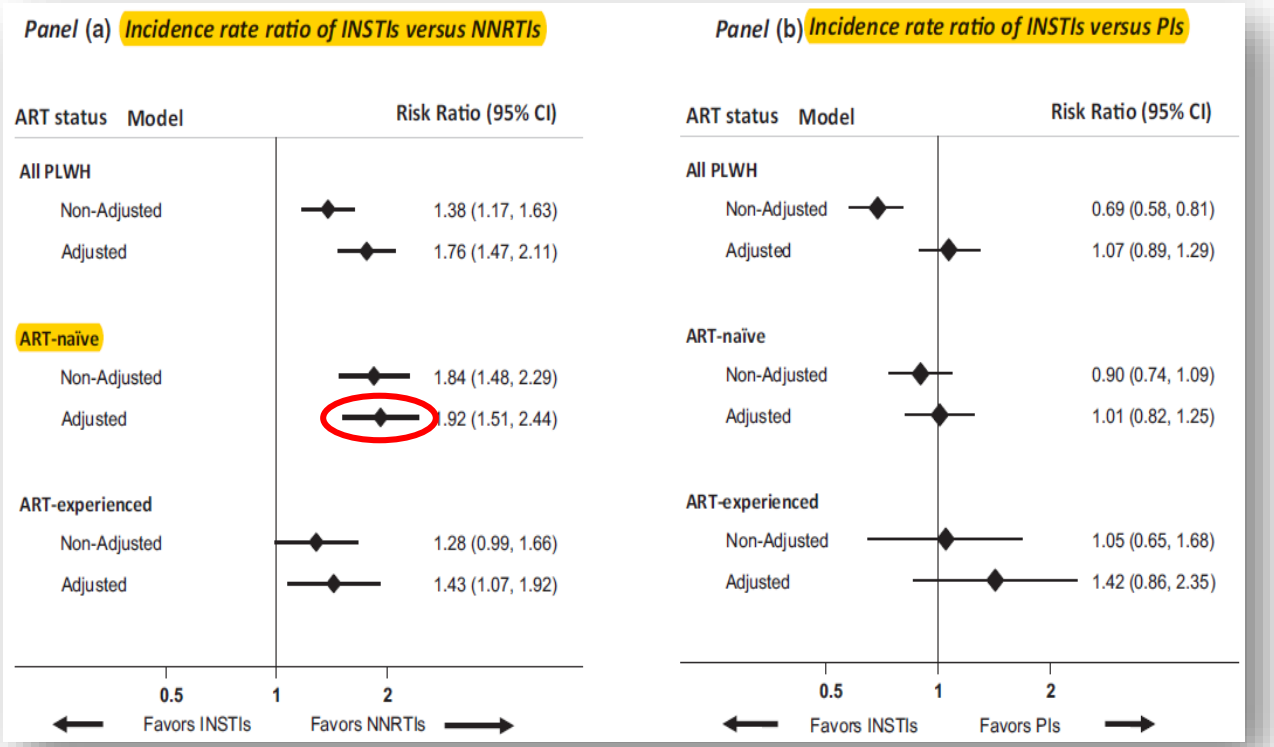
Variation in BG are not significantly different in PLWH starting for the first time BIC vs DTG therapy at a follow-up of 12 months. To be Naïve or Experienced to Antiretroviral treatment does not have a significant impact on BG variation in this cohort.

Incidence of **hypertension** in people with HIV who are treated with **integrase inhibitors** versus other antiretroviral regimens in the **RESPOND** cohort consortium

RESULTS

- BL systolic BP 120 mmHg,
- BL diastolic BP 78 mmHg
- BL age 43 years

- Over 8380.4 person-years **23.0% participants developed hypertension.**
- **Participants receiving INSTIs had a higher incidence of hypertension** than those receiving NNRTIs (aIRR 1.76)
- The incidence was **no different in those receiving PIs** (aIRR 1.07)
- Prior **AIDS, CD4 count <350 cells/µl, ART naïve, age>5-years increase** and **obesity** were predictors of hypertension.



Byonanebye DM et al_HIV Medicine 2022

Incidence of **hypertension** in people with HIV who are treated with **integrase inhibitors** versus other antiretroviral regimens in the **RESPOND** cohort consortium

•*DISCUSSION*

- There is an association between the use of INSTIs and **weight gain, a key risk factor for hypertension**.
- The use of **INSTIs** has also been associated with **adipogenesis, oxidative stress and insulin resistance** and these metabolic derangements have **been associated with hypertension**.
- Additional studies have linked INSTIs with other predictors of hypertension such as **dyslipidaemia and diabetes mellitus**.
- **Did not find a significant association** between incident hypertension and other previously reported risk factors such as diabetes and abnormal lipid levels. These risk factors may **require longer exposure** to have an impact on BP.
- Few participants were receiving **bictegravir, cabotegravir, or doravirine**, which were excluded from the analysis.

➢ Although unmeasured confounding and channelling bias cannot be excluded, INSTIs were associated with a higher incidence of hypertension than were NNRTIs, but rates were similar to those of PIs overall, in ART-naïve and ART-experienced participants within RESPOND.

•Byonanebye DM et al_HIV Medicine 2022

Recently **published evidence** about to **cardiometabolic outcomes** associated to ART

OUTCOME MEASURE	AUTHOR	PUBLICATION/PRESENTATION	YEAR	N	OUTCOME
BMI	Bansi-Matharu et al.	Lancet HIV, 2021;September:S2352	2021	14703	Compared with 3TC; **DTG (OR 1.27), RAL (OR 1.37), and TAF (OR 1.38)** were significantly associated with more than **7% BMI increase**
DYSLIPIDEMIA	Byonanebye DM et al.	AIDS 2021, 35:869–882	2021	4577	Participants taking **InSTI** had a lower incidence of dyslipidemia compared with those on PI/b (adjusted IRR 0.71), but **higher rate compared with those on NNRTI (1.35).**
HYPERTENSION	Byonanebye DM et al.	HIV Med. 2022 Mar	2022	4606	PLWH receiving **InSTI** had a **76% higher incidence of HTN** than those receiving NNRTIs **(aIRR=1.76)**
DIABETES MELLITUS	O'Halloran JA et al.	CID, 2022; ciac355, https://doi.org/10.1093/cid/ciac355	2022	42382	PWH starting an **InSTI** were **31% more likely to develop DM** vs. those starting a non-INSTI (NNRTI or PI)
NAFLD progression	Bischoff J, et al.	EClinicalMedicine. 2021 Sep 5;40:101116	2021	319	A **BMI>23 kg/m^2 (OR: 4.24), TAF (OR: 5.07); and InSTI (OR: 2.35), as well as type 2 DM (OR: 7.61)** were independent predictors of ***de novo* steatosis** in multivariable analysis
CV EVENTS	Neesgaard et al.	Lancet HIV. 2022 Jun 7:S2352-3018(22)00094-7.	2022	29340	**InSTI** exposure was associated with an **aIRR of 1.85** for CVD events in the first 6 months after InSTI initiation compared with no exposure
CV EVENTS	Donga et al	AIDS2022 EPB108	2022	14076	Patients initiating **InSTI** were significantly more likely to experience **congestive heart failure (HR=2.12), myocardial infarction (HR=1.79), and lipid disorders (HR=1.26)** than those initiating non-InSTI.

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Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium

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See Comment page e451

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Summary

Background Although associations between older antiretroviral drug classes and cardiovascular disease in people living with HIV are well described, there is a paucity of data regarding a possible association with integrase strand-transfer inhibitors (INSTIs). We investigated whether exposure to INSTIs was associated with an increased incidence of cardiovascular disease.

Methods RESPOND is a prospective, multicentre, collaboration study between 17 pre-existing European and Australian cohorts and includes more than 32 000 adults living with HIV in clinical care after Jan 1, 2012. Individuals were eligible for inclusion in these analyses if they were older than 18 years, had CD4 cell counts and HIV viral load measurements in the 12 months before or within 3 months after baseline (latest of cohort enrolment or Jan 1, 2012), and had no exposure to INSTIs before baseline. These individuals were subsequently followed up to the earliest of the first cardiovascular disease event (ie, myocardial infarction, stroke, or invasive cardiovascular procedure), last follow-up, or Dec 31, 2019. We used multivariable negative binomial regression to assess associations between cardiovascular disease and INSTI exposure (0 months [no exposure] *vs* >0 to 6 months, >6 to 12 months, >12 to 24 months, >24 to 36 months, and >36 months), adjusted for cardiovascular risk factors. RESPOND is registered with ClinicalTrials.gov, NCT04090151, and is ongoing.

Findings 29 340 people living with HIV were included in these analyses, of whom 7478 (25·5%) were female, 21 818 (74·4%) were male, and 44 (<1%) were transgender, with a median age of 44·3 years (IQR 36·2–51·3) at baseline. As of Dec 31, 2019, 14 000 (47·7%) of 29 340 participants had been exposed to an INSTI. During a median follow-up of 6·16 years (IQR 3·87–7·52; 160 252 person-years), 748 (2·5%) individuals had a cardiovascular disease event (incidence rate of 4·67 events [95% CI 4·34–5·01] per 1000 person-years of follow-up). The crude cardiovascular disease incidence rate was 4·19 events (3·83–4·57) per 1000 person-years in those with no INSTI exposure, which increased to 8·46 events (6·58–10·71) per 1000 person-years in those with more than 0 months to 6 months of exposure, and gradually decreased with increasing length of exposure, until it decreased to similar levels of no exposure at more than 24 months of exposure (4·25 events [2·89–6·04] per 1000 person-years among those with >24 to 36 months of exposure). Compared with those with no INSTI exposure, the risk of cardiovascular disease was increased in the first 24 months of INSTI exposure and thereafter decreased to levels similar to those never exposed (>0 to 6 months of exposure: adjusted incidence rate ratio of 1·85 [1·44–2·39]; >6 to 12 months of exposure: 1·19 [0·84–1·68]; >12 to 24 months of exposure: 1·46 [1·13–1·88]; >24 to 36 months of exposure: 0·89 [0·62–1·29]; and >36 months of exposure: 0·96 [0·69–1·33]; p<0·0001).

Interpretation Although the potential for unmeasured confounding and channelling bias cannot fully be excluded, INSTIs initiation was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors. These early findings call for analyses in other large studies, and the potential underlying mechanisms explored further.

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Self-control for harm reduction in chemsex

We read with interest Carol Strong and colleagues' comprehensive Review of harm-reduction interventions to address chemsex as part of the portfolio to prevent transmission of HIV and sexually transmitted infections.[1] We would like to raise three points related to our work that is cited in the Review. First, although the authors acknowledge the use of our journey model towards problematic chemsex,[2] they note that "such an approach might risk assuming a linear, simplistic pathway in which harms are encountered by people using drugs".[1] We contend that this risk is unlikely because we explicitly defined this process as "a common pattern of events, rather than an inevitable progression".[2] Second, although we welcome the overview of interventions on various dimensions of harm reduction, the Review remains focused on medical interventions. Such a focus obscures chemsex users' psychological toolbox to adapt their behaviour. Instead, Strong and colleagues describe what people can do to reduce their risk, but do not provide the tools to reduce risky behaviour. Reducing experienced adverse effects associated with sexualised drug use was the topic of a framework in which we conceptualised self-control to understand and support people who engage in chemsex.[3] Finally, in the introduction of the Review, Strong and colleagues state that "chemsex refers to a planned behaviour with a clear intent to use specific drugs to enhance the sexual experience".[1] We challenge this assumption, as argued in our conceptual framework on self-control.[3] The available evidence suggests that, as people progress through their chemsex journey, automatic and cue-driven processes come to dominate substance use,[3] representing automatic over planned or reasoned processes.

We declare no competing interests.

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Tenofovir disoproxil fumarate withdrawal and cardiovascular risk

We read with great interest Bastian Neesgaard and colleagues'[1] report about temporarily increased atherosclerotic cardiovascular disease risk in people living with HIV who initiated integrase strand transfer inhibitor (INSTI) treatment. Neesgaard and colleagues' model only controlled for exposure to antiretrovirals previously associated with atherosclerotic cardiovascular disease risk but not for tenofovir disoproxil fumarate use.

Tenofovir disoproxil fumarate initiation in people living with HIV on stable antiretroviral therapy leads to decreased serum cholesterol,[2] whereas its substitution with tenofovir alafenamide is associated with cholesterol and weight increases.[3] Because most proprietary INSTI-based single tablet regimens in Europe did not contain tenofovir disoproxil fumarate after 2015, switching to an INSTI-based single tablet regimen could have often coincided with tenofovir disoproxil fumarate discontinuation. It would be informative to know the proportion of these patients among patients initiating INSTI treatment in Neesgaard and colleagues' analysis.

Based on a comparative multilevel marginal structural model built on 1-year percentages of days covered, we previously reported substantially lower all-cause mortality and atherosclerotic cardiovascular disease events during consistent use of lipid-lowering therapy.[4] We had studied 23 276 US veterans living with HIV who had reached virological suppression on antiretrovirals from 1997 to 2011 (before widespread INSTI use).[4] With the same cohort and methods, we built two new multivariable Cox survival models to examine the effects of different tenofovir disoproxil fumarate exposure levels on the risk of acute atherosclerotic cardiovascular disease events during and within 6 months after exposure.

	Events	Patient years	Adjusted hazard ratio	95%CI	p value
During TDF exposure					
No TDF exposure within the past year	787	75 390	1 (ref)	..	..
TDF 1 year–PDC <80%	307	29 732	0·93	0·80–1·07	0·31
TDF 1 year–PDC ≥80%	210	30 178	0·79	0·66–0·95	0·012
Within 6 months of TDF discontinuation					
No TDF discontinuation within 6 months	1177	123 696	1 (ref)	..	..
Previous TDF 1 year–PDC <80%	78	8497	0·89	0·71–1·13	0·34
Previous TDF 1 year–PDC ≥80%	49	3622	1·48	1·11–1·98	0·0079

PDC=percentages of days covered. TDF=tenofovir disoproxil fumarate.

Table: Risk for acute atherosclerotic cardiovascular disease event

The models were stratified by lipid-lowering therapy use (administered within the last year) and prevalent cardiovascular disease and adjusted for 23 traditional, HIV, and cohort-specific time-variable weekly-updated covariates. We used International Classification of Disease–9 codes and procedure codes, laboratory values, and radiology examinations to define acute atherosclerotic cardiovascular disease events.[4] Over a median follow-up of 5 years, 1304 veterans had an acute atherosclerotic cardiovascular disease event (877 coronary, 434 cerebrovascular, and seven with both events). Consistent and ongoing tenofovir disoproxil fumarate exposure (≥80% of days covered) was associated with a 21% decreased risk for acute atherosclerotic cardiovascular disease events but risk increased 48% during the first 6 months after tenofovir disoproxil fumarate discontinuation (table). Other important predictors included: age, calendar year, BMI, chronic kidney disease, hepatitis C, anaemia, very low CD4 cell count, detectable HIV viraemia, and consistent abacavir use.

Our analysis suggests that tenofovir disoproxil fumarate discontinuation among people living with HIV with previous 1-year exposure greater than 80% could explain at least part of the observed temporary association between INSTI initiation and atherosclerotic cardiovascular disease risk.[1]

BB reports grants and consulting fees from Merck and ViiV, advising fees from Gilead Sciences and Janssen. HD and CA declare no competing interests.

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2 Tungsiripat M, Kitch D, Ginsky MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS* 2010; **24**: 1781–84.
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Authors' reply

Henning Drechsler and colleagues suggest that discontinuation of tenofovir disoproxil fumarate due to increased availability of single tablet regimens without the drug might elevate cardiovascular disease risk due to serum lipid increases; explaining at least some of the association between integrase strand transfer inhibitors (INSTIs) exposure and cardiovascular disease found in our study within the RESPOND cohort.[1]

In our study, we followed up individuals from 2012, until first cardiovascular disease event, last follow-up, or the end of 2019. Although use of tenofovir disoproxil fumarate might have decreased in the USA after 2015, previous RESPOND reports have found that tenofovir disoproxil fumarate with emtricitabine was the second most commonly used backbone (after abacavir with lamivudine) for those initiating dolutegravir, and the most common for those starting elvitegravir or raltegravir by Oct 1, 2012,[2] whereas exposure to tenofovir alafenamide was limited to less than 15% of participants.[3] Drechsler and colleagues[4] analysed the period 1996–2011, before tenofovir alafenamide and second-generation INSTIs were available, and it is unclear from their letter which backbone was most commonly initiated after tenofovir disoproxil fumarate discontinuation. Although we note that their analysis controls for abacavir use, it would be of interest to know how many initiated abacavir, as it might explain at least some of tenofovir disoproxil fumarate's cardioprotective effects found by Drechsler and colleagues.

We did not include adjustments for tenofovir disoproxil fumarate and tenofovir alafenamide in our primary model, as neither has reliably been linked with cardiovascular disease. However, in exploratory univariate analyses, cumulative exposure to neither drug (per 5 years of exposure) was significantly associated with cardiovascular disease among over 29 000 included individuals (p=0·86 and p=0·29, respectively), although with limited statistical power for tenofovir alafenamide. Moreover, some studies further suggest that tenofovir disoproxil fumarate lowers both the harmful LDL cholesterol and the beneficial HDL cholesterol.[5] Regardless, we found no indication that the increased cardiovascular disease risk with INSTI exposure was mediated by dyslipidaemia or BMI, reflected by no effect of adjusting for these as time-updated variables.[1] This finding would be consistent with existing knowledge about dyslipidaemia (on its own or exacerbated by tenofovir disoproxil fumarate discontinuation) causing cardiovascular disease via a slower atherosclerotic process,[6] contrasting our findings of increased cardiovascular disease risk within the first 6–24 months of INSTI exposure. Finally, a common reason for tenofovir disoproxil fumarate discontinuation is declining estimated glomerular filtration rate and proteinuria, which are independently associated with increased cardiovascular disease risk.[7,8]

In our study, tenofovir disoproxil fumarate remained a common backbone used across Australian and European cohorts after 2015, and cumulative exposure was not associated with cardiovascular disease in our analysis—neither directly in exploratory analyses nor indirectly when adjusting for dyslipidaemia and BMI increase, which might be a

Associations between **integrase strand-transfer inhibitors** and **cardiovascular disease** in people living with HIV: a multicentre prospective study from the **RESPOND** cohort consortium

RESULTS

- **29 340 PLWH** included: **74.4% male**, median age **44.3 years**.
- As of **Dec 31, 2019**, **47.7%** of participants had been exposed to an **INSTI**: 8647 **DTG (>50%)**, 3344 ELV/c, 3296 RAL, 840 BIC.
- FU of **6.16 years: 2.5%** individuals had a **cardiovascular disease event**.
- Crude cardiovascular disease incidence rate:
  - **No INSTI exposure** → **4.19** events per 1000 person-years in those with,
  - **More than 0 months to 6 months of exposure** → **8.46** events per 1000 person-years,
  - **>24 to 36 months** of exposure → **4.25 events per 1000 person-years.**
- Compared with those with no INSTI exposure, risk of cardiovascular disease, **increased in the first 24 months of INSTI exposure** and **thereafter decreased** to levels similar to those never exposed.

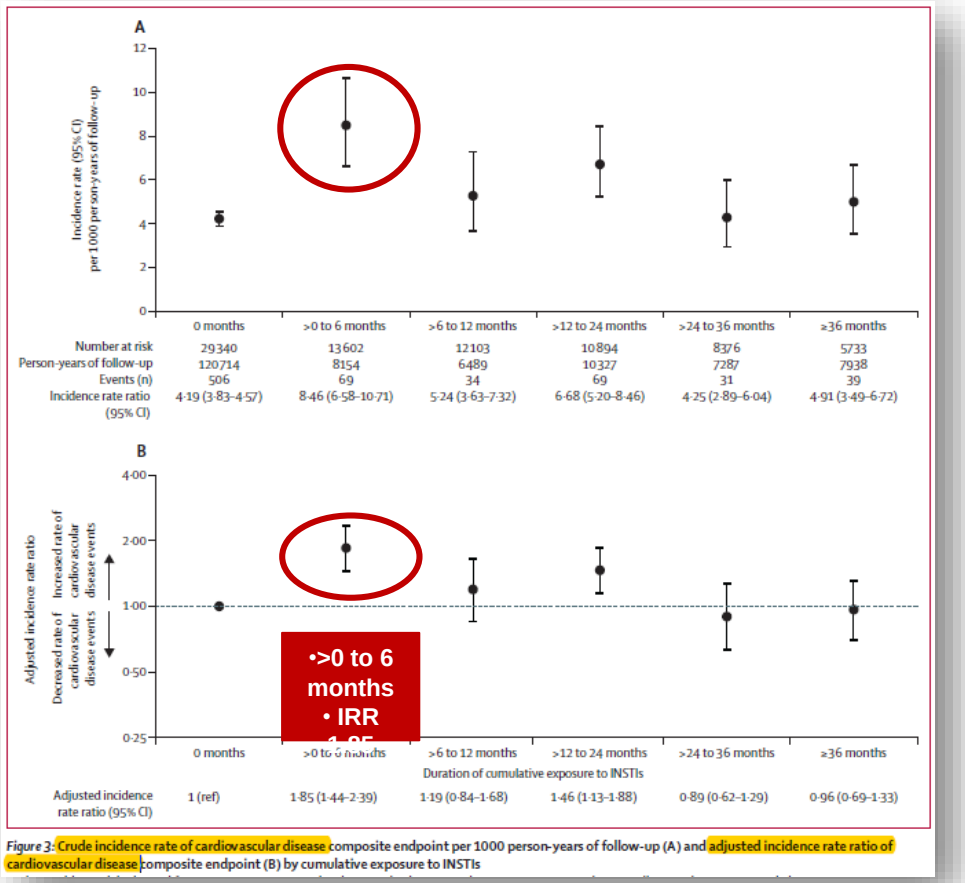

Figure 3: Crude incidence rate of cardiovascular disease composite endpoint per 1000 person-years of follow-up (A) and adjusted incidence rate ratio of cardiovascular disease composite endpoint (B) by cumulative exposure to INSTIs

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Associations between **integrase strand-transfer inhibitors** and **cardiovascular disease** in people living with HIV: a multicentre prospective study from the **RESPOND** cohort consortium

OVERALL AND **SENSITIVITY ANALYSES**

Adjusted incidence rate ratio of the CVD composite endpoint by cumulative exposure to INSTIs, compared with no INSTI exposure

	> 0 to 6 months	>6 to 12 months	>12 to 24 months	>24 to 36 months	>36 months	p
Primary model	**1.85 (1.44-2.39)**	1.19 (0.84-1.68)	**1.46 (1.13-1.88)**	0.89 (0.62-1.29)	0.96 (0.69-1.33)	<0.001
Model with time-updated factors on the potential causal pathway	**1.92 (1.47-2.52)**	1.09 (0.74-1.61)	1.27 (0.95-1.70)	0.81 (0.54-1.22)	0.87 (0.61-1.26)	<0.001
Model (potential causal pathway and platelets)	**1.93 (1.47-2.52)**	1.09 (0.74-1.61)	1.27 (0.95-1.70)	0.82 (0.54-1.23)	0.88 (0.61-1.27)	<0.001
Model only adjusted for DAD CVD risk score	**2.07 (1.61-2.66)**	1.29 (0.91-1.83)	**1.61 (1.25-2.07)**	1.00 (0.70-1.45)	1.11 (0.80-1.53)	<0.001
Excluding PLWH with previous CVD event	**1.83 (1.39-2.41)**	1.12 (0.77-1.63)	**1.36 (1.03-1.80)**	0.86 (0.58-1.28)	0.97 (0.69-1.38)	<0.001
Excluding from events invasive CVD procedures	**1.77 (1.30-2.41)**	1.13 (0.74-1.73)	**1.55 (1.15-2.08)**	0.73 (0.45-1.17)	0.93 (0.63-1.38)	<0.001
Only PLWH who started or switched ART after 2012	**1.76 (1.31-2.37)**	1.18 (0.82-1.71)	**1.41 (1.05-1.89)**	0.98 (0.68-1.43)	1.03 (0.72-1.46)	0.002
Including only centrally adjudicated CVD events	1.37 (0.89-2.12)	1.30 (0.82-2.06)	1.33 (0.93-1.90)	0.93 (0.61-1.42)	0.88 (0.59-1.31)	0.22

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Associations between **integrase strand-transfer inhibitors** and **cardiovascular disease** in people living with HIV: a multicentre prospective study from the **RESPOND** cohort consortium

DISCUSSION

- **First assessment of INSTI exposure and cardiovascular disease events** to use data derived from a large and multinational cohort.
- The association INSTI/CVD events appeared **similar in individuals with high and low estimated cardiovascular disease risk** and across a **wide range of sensitivity analyses**.
- Because **increased BMI** is associated with cardiovascular disease, INSTI exposure could potentially increase cardiovascular disease risk **over time.**
- The absence of an attenuated effect **after adjusting for BMI and other known risk factors** for cardiovascular disease suggests **different possible explanations**:

1. **Not captured the risk factors** for cardiovascular disease or **unmeasured risk factors** in the INSTI-exposed popula
2. INSTIs can increase rates of cardiovascular disease events via a **different mechanism unrelated to known risk fac** (e.g. drug-induced platelet hyper-reactivity, or the antibody-mediated clot formation and thrombocytopenia)

➢ Although the potential for unmeasured confounding and channelling bias cannot fully be excluded, INSTIs initiation was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors.

Io c’ero!

HIV Medicine
Original Article

Subclinical atherosclerosis as detected by carotid ultrasound and associations with cardiac and HIV specific risk factors; the Archi-Prevaleat project

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Among 1147 evaluated patients, aged 50 years on average, 347 (30.2%) had pathological findings (15.8% plaques and 14.5% IMT). Besides usual risk factors, such as older age, male sex, overweight and dyslipidemia, CD4+ cell nadir <200 cells/mL was associated with higher prevalence of plaques (adjusted OR 1.79, 95% CI 1.23-2.61). INSTI use was suggested as associated with pathological findings.

Table 1. Main characteristics of 1147 HIV-positive patients included in the baseline analysis, according to the presence of plaques.

	Normal N=800, 69.8%	IMT 1.01-1.20 N=166, 14.5%	Plaques N=181, 15.8%	P
Age (years), mean ± SD	50.0 ± 9.7	55.1 ± 9.1	58.2 ± 9.1	<0.0001
Male, n (%)	632 (79.0)	146 (88.0)	163 (90.1)	<0.0001
Risk for HIV acquisition, n (%)				
IDU	103 (12.9)	23 (13.9)	27 (14.9)	
Sexual	513 (64.1)	89 (53.6)	109 (60.2)	
Other	184 (23.0)	54 (32.5)	45 (24.9)	0.64
Smoking habits, n (%)				
Never	172 (21.5)	31 (18.7)	28 (15.5)	
Current	311 (38.9)	72 (43.4)	66 (36.5)	
Former	153 (19.1)	40 (24.1)	45 (24.9)	
Unknown	164 (20.5)	23 (13.9)	42 (23.2)	0.65
BMI (kg/m2), mean ± SD	24.6 ± 3.7	24.9 ± 3.9	25.6 ± 3.9	0.006
BMI class (kg/m2), n (%)				
<18.5	22 (2.8)	2 (1.2)	4 (2.2)	
18.5-25.0	411 (51.4)	81 (48.8)	73 (40.3)	
>25.0-30.0	234 (29.2)	49 (29.5)	68 (37.6)	
>30.0	55 (6.9)	14 (8.4)	21 (11.6)	0.001
missing	78 (9.8)	20 (12.0)	15 (8.3)	
Cardiovascular diseases, n (%)				
Hypertension	237 (29.6)	70 (42.2)	96 (53.0)	<0.0001
Diabetes	60 (7.5)	15 (9.0)	35 (19.3)	<0.0001
Ictus	8 (1.0)	2 (1.2)	5 (2.8)	0.08
Angina	3 (0.4)	0	5 (2.8)	0.003
IMA	10 (1.2)	6 (3.6)	6 (3.3)	0.02
PAD	3 (0.4)	1 (0.6)	3 (1.7)	0.06
HCV coinfection, n (%)	209 (26.1)	58 (34.9)	56 (30.9)	0.06
Systolic blood pressure (mm Hg), mean ± SD	125.2 ± 15.4	126.8 ± 15.8	130.1 ± 16.3	0.0009
Diastolic blood pressure (mm Hg), mean ± SD	79.2 ± 10.3	80.6 ± 10.8	78.8 ± 11.1	0.25
Cholesterol (mg/dL), mean ± SD	190 ± 41	187 ± 39	192 ± 41	0.57
HDL-C (mg/dL), mean ± SD	50 ± 17	46 ± 13	45 ± 19	0.004
LDL-C (mg/dL), mean ± SD	119 ± 37	119 ± 34	119 ± 36	0.99
Triglycerides (mg/dL), median (IQR)	120 (86-171)	113 (86-175)	157 (100-214)	<0.0001
Blood glucose§ (mg/dL), mean ± SD	88 ± 12	89 ± 12	93 ± 17	<0.0001
AST (U/L), median (IQR)	24 (19-32)	24 (20-32)	27 (21-36)	0.02
ALT (U/L), median (IQR)	29 (22-43)	28 (22-42)	31 (23-45)	0.59
eGFR (mL/min), mean ± SD	95.9 ± 17.3	91.6 ± 17.1	91.3 ± 22.4	0.001

HCV coinfection, n (%)	209 (26.1)	58 (34.9)	56 (30.9)	0.06
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ALT (U/L), median (IQR)	29 (22-43)	28 (22-42)	31 (23-45)	0.59
eGFR (mL/min), mean ± SD	95.9 ± 17.3	91.6 ± 17.1	91.3 ± 22.4	0.001
HIV infection duration (years),	13.9 ± 3.8	14.6 ± 2.9	14.5 ± 4.6	0.04
Nadir CD4 (cells/mL), median (IQR)	223 (127-229)	207 (100-323)	141 (90-272)	0.002
Current CD4 (cells/mL), median (IQR)	715 (522-919)	686 (486-936)	687 (498-904)	0.63
Current CD8 (cells/mL), * median (IQR)	888 (652-1190)	839 (597-1123)	895 (641-1212)	0.52
CD4/CD8 ratio, * median (IQR)	0.81 (0.54-1.16)	0.82 (0.53-1.09)	0.73 (0.46-1.15)	0.62
Naive, n (%)	17 (2.1)	0	0	0.01
NRTI, n (%)				
Current use	673 (84.1)	134 (80.7)	151 (83.4)	0.60
Past use	601 (75.1)	126 (75.9)	125 (69.1)	0.14
PI, n (%)				
Current use	378 (47.2)	80 (48.2)	91 (50.3)	0.46
Past use	377 (47.1)	83 (50.0)	94 (51.9)	0.21
NNRTI, n (%)				
Current use	263 (32.9)	57 (34.3)	48 (26.5)	0.17
Past use	243 (30.4)	55 (33.1)	40 (22.1)	0.08
InSTI, n (%)				
Current use	166 (20.8)	39 (23.5)	56 (30.9)	0.004
Past use	132 (16.5)	35 (21.1)	33 (18.2)	0.35

Table 2. Details of ARV treatment in 1147 HIV-positive patients included in the baseline analysis, according to the presence of plaques.

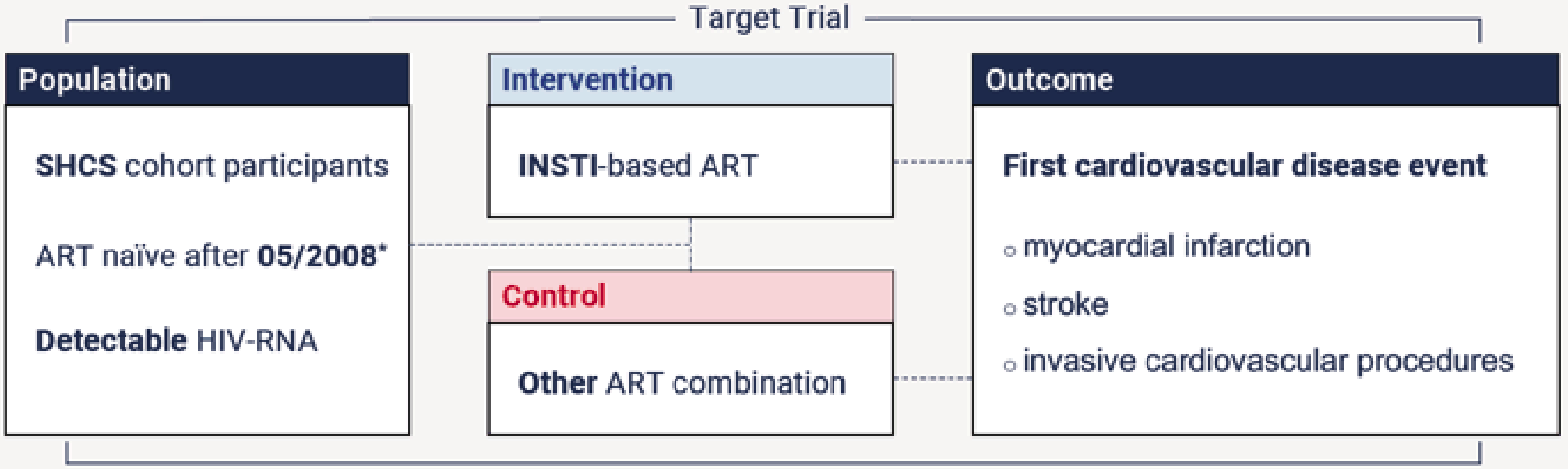
	Normal N=800, 69.8%	IMT 1.01-1.20 N=166, 14.5%	Plaques N=181, 15.8%	P
Current NRTI, n (%)				
Tenofovir	380 (47.5)	79 (47.6)	80 (44.2)	0.47
Abacavir	198 (24.7)	34 (20.5)	48 (26.5)	0.92
Lamivudine	294 (36.8)	55 (33.1)	71 (39.2)	0.76
Current PI, n (%)				
Atazanavir	175 (21.9)	35 (21.1)	42 (23.2)	0.78
Darunavir	169 (21.1)	41 (24.7)	38 (21.0)	0.79
Current NNRTI, n (%)				
Efavirenz	103 (12.9)	20 (12.0)	21 (11.6)	0.61
Current InSTI, n (%)				
Raltegravir	65 (8.1)	24 (14.5)	30 (16.6)	0.0002
Dolutegravir	72 (9.0)	11 (6.6)	19 (10.5)	0.78
Elvitegravir	29 (3.6)	4 (2.4)	7 (3.9)	0.92

Impact of integrase inhibitors on cardiovascular disease events in people with HIV starting antiretroviral therapy

Bernard Surial ✉, Frédérique Chammartin, José Damas, Alexandra Calmy, David Haerry, Marcel Stöckle, Patrick Schmid, Enos Bernasconi, Christoph A Fux, Philip Tarr, Huldrych F Günthard, Gilles Wandeler, Andri Rauch, the Swiss HIV Cohort Study

Clinical Infectious Diseases, ciad286, https://doi.org/10.1093/cid/ciad286
Published: 09 May 2023 **Article history** ▾

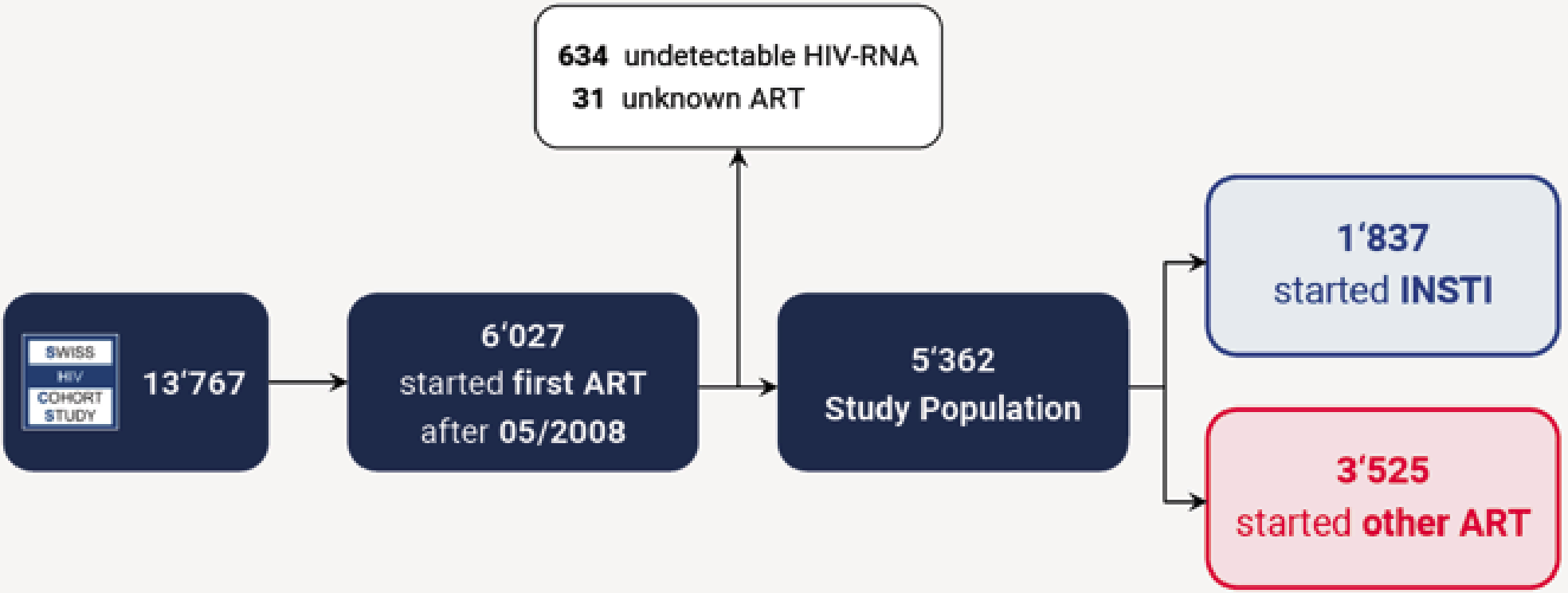
Methods



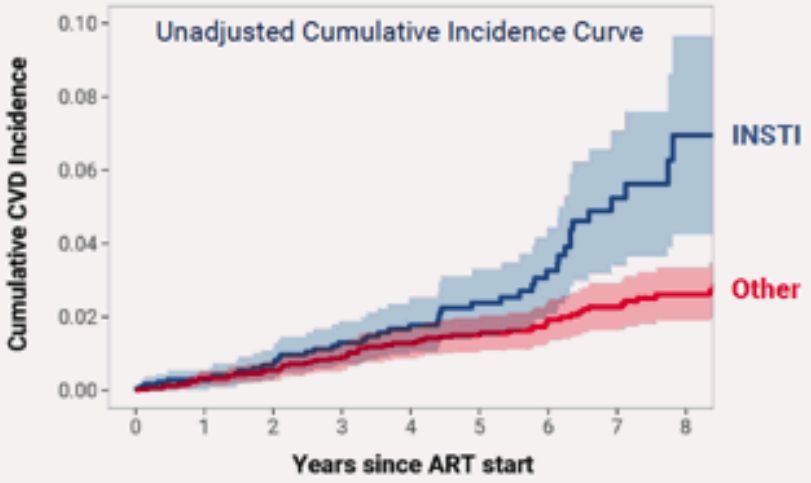
- Individuals who stopped the intended strategy were **artificially censored**
- Pooled logistic regression models
- Adjustments with **inverse probability of treatment and censoring weights**

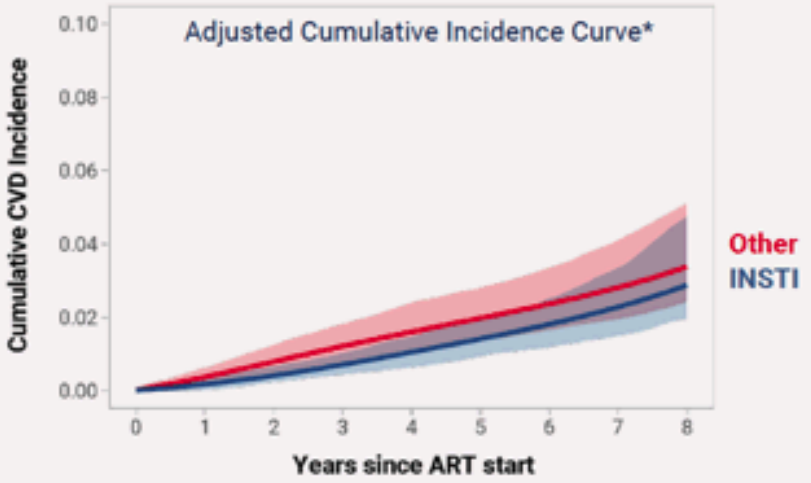
**Introduction of INSTI in Switzerland*

Selection of Population



116 CVD events within 4.9 years (IQR 2.4–7.4)





Number at risk

INSTI	1813	1615	1398	1165	945	722	504	275	130
Other	3549	3161	2855	2522	2227	1933	1582	1261	976

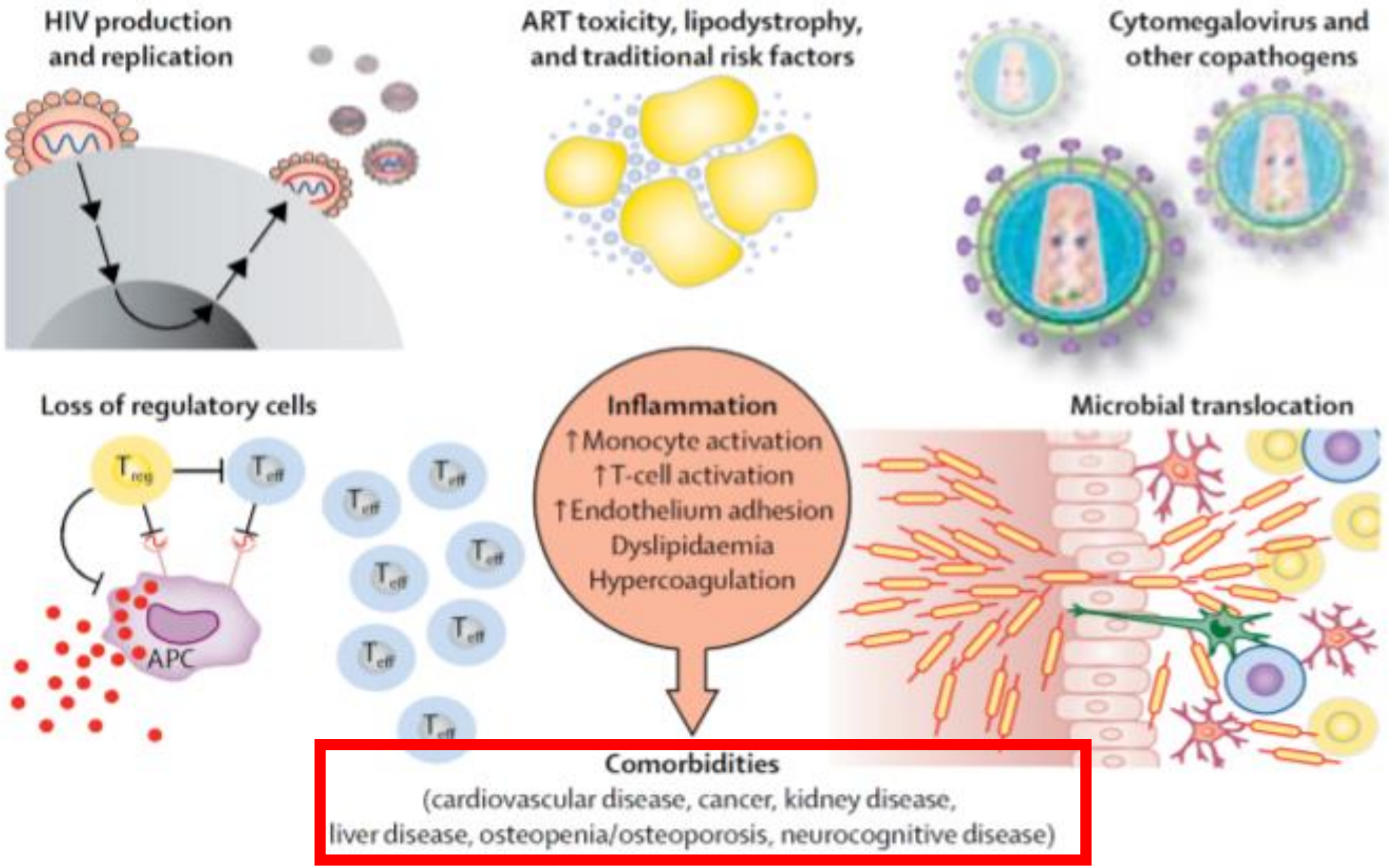
**Adjusted for calendar year, age, sex, ethnicity, HIV transmission group, highest education, CD4 cell count, HIV viral load , personal and family history of cardiovascular disease, body mass index, arterial hypertension, diabetes, renal function, current use of antiplatelet or lipid-lowering drugs, and current use of abacavir or tenofovir alafenamide.*

Surial B

*Adjusted for calendar year, age, sex, ethnicity, HIV transmission group, highest education, CD4 cell count, HIV viral load , personal and family history of cardiovascular disease, body mass index, arterial hypertension, diabetes, renal function, current use of antiplatelet or lipid-lowering drugs, and current use of abacavir or tenofovir alafenamide.

Conclusions

- Rapid **uptake of INSTI as initial ART** in Switzerland
- **No difference of cardiovascular disease events** between treatment-naïve individuals starting INSTI and those starting other ART
- Similar studies are needed in treatment-experienced individuals **switching to INSTI**



Deeks, Lancet 201

REPRIEVE
Randomized Trial to Prevent Vascular Events in HIV

NIH National Institutes of Health
Turning Discovery Into Health

NEWS RELEASES

Tuesday, April 11, 2023

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

The study participants had no prior history of atherosclerotic cardiovascular disease and had comorbidities and laboratory values (including cholesterol and triglyceride levels) consistent **with low to moderate CVD risk — a population that would not normally be advised to take statins.**

(…)

At its most recent meeting, the board recommended that the study **should be stopped early** because the statin was already showing a clear benefit. **Participants who took pitavastatin had a 35% lower risk for major cardiovascular events**, making it unethical to keep some participants on the placebo.

Grazie per l'attenzione

- ***«Vi è un'età in cui si insegna ciò che si sa;***
- ***Ma poi ne viene un'altra in cui si insegna ciò che non si sa: e questo si chiama fare ricerca»***

- *R. Barthes*