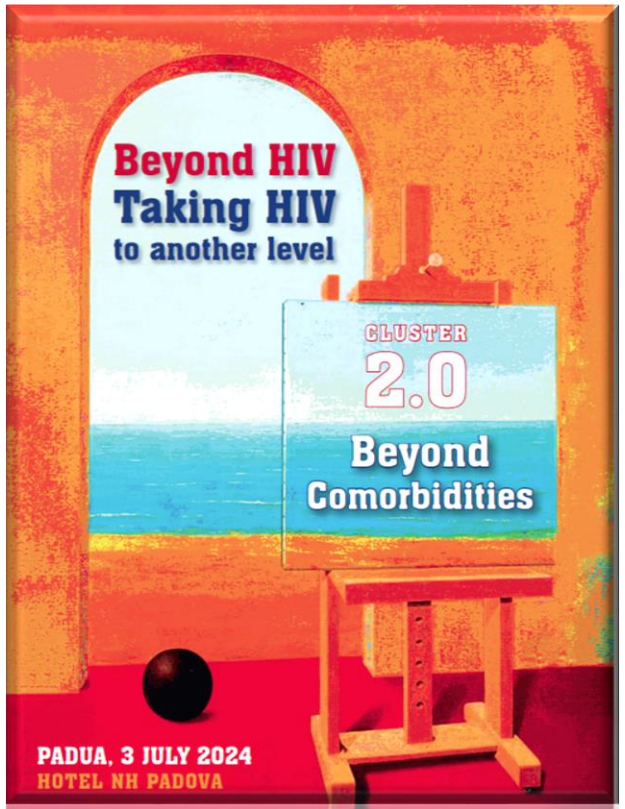


Clinical Review on management of cardiovascular disease

Paolo Maggi

Università della Campania, Luigi Vanvitelli

UOC Malattie Infettive e Tropicali AORN Caserta

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

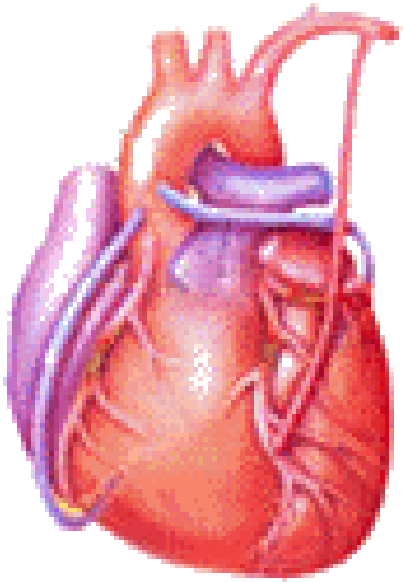
ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

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

CVD in PWH, a real problem?



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

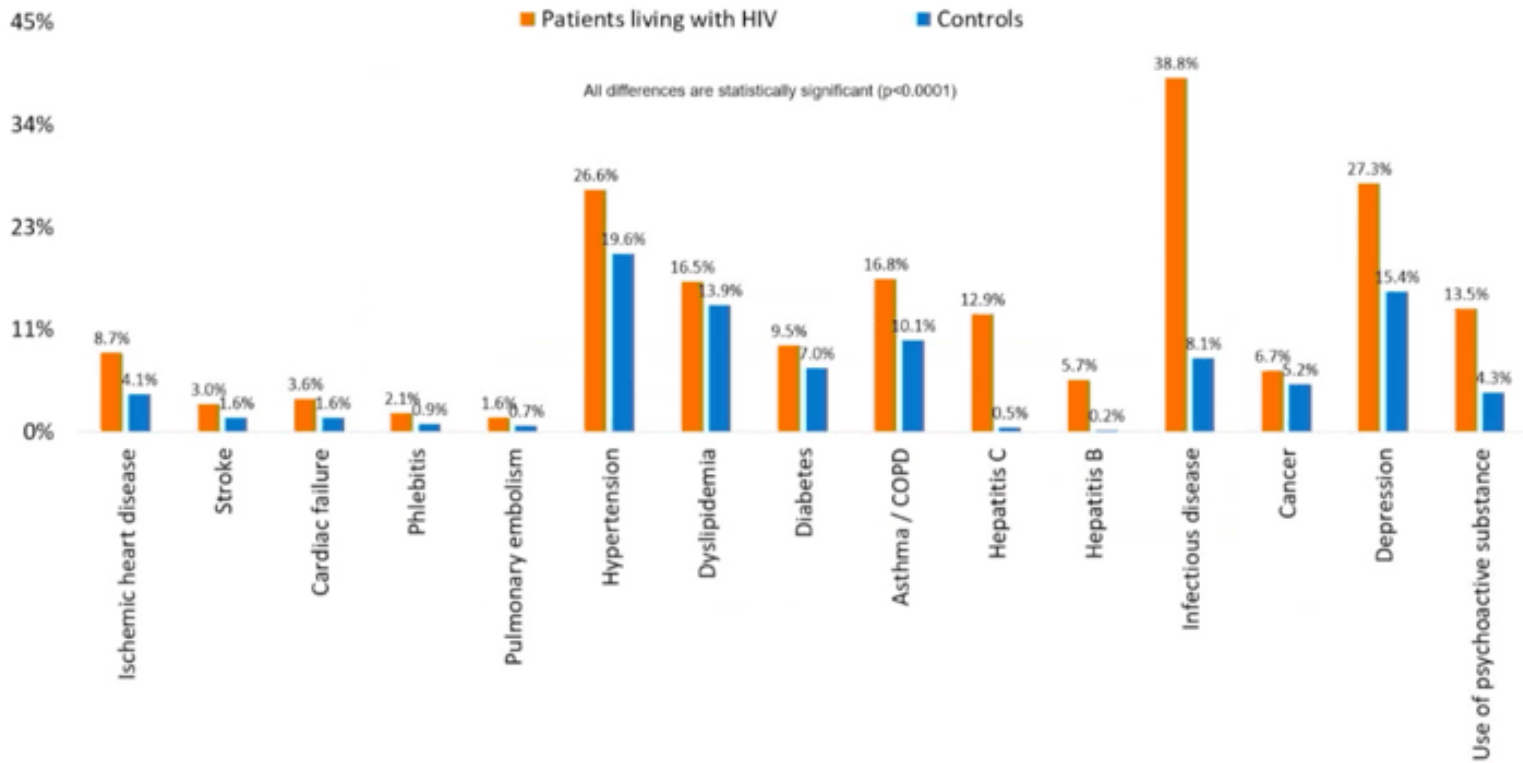
HOPITAL FOCH

HCL

CEMKA

Groupe — Control Group — PLHIV

COMORBIDITIES AND RISK FACTORS
PLHIV VERSUS FRENCH POPULATION



IMPACT of COMORBIDITIES on DEATHS

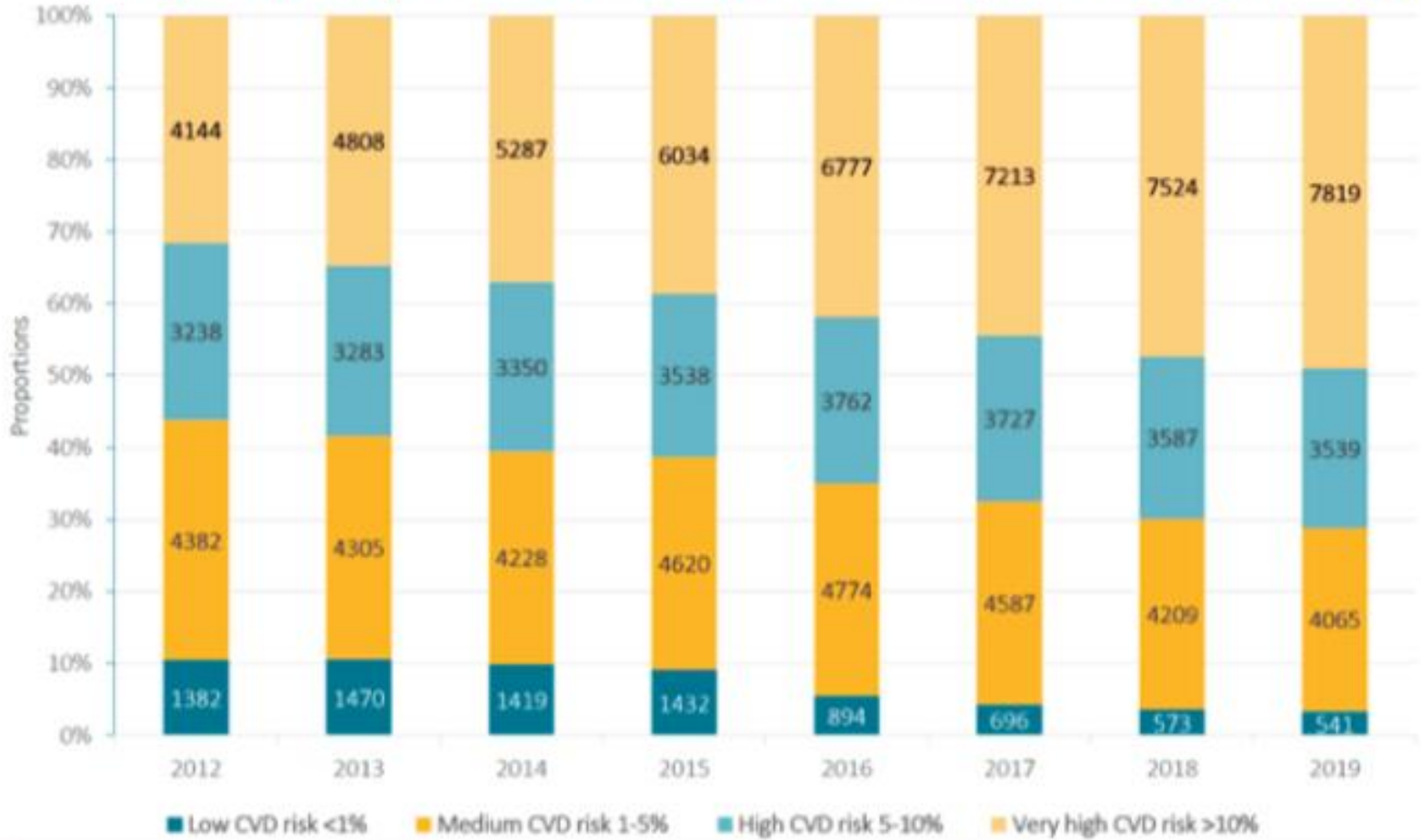
HIV Drug Therapy
GLASGOW 2022

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

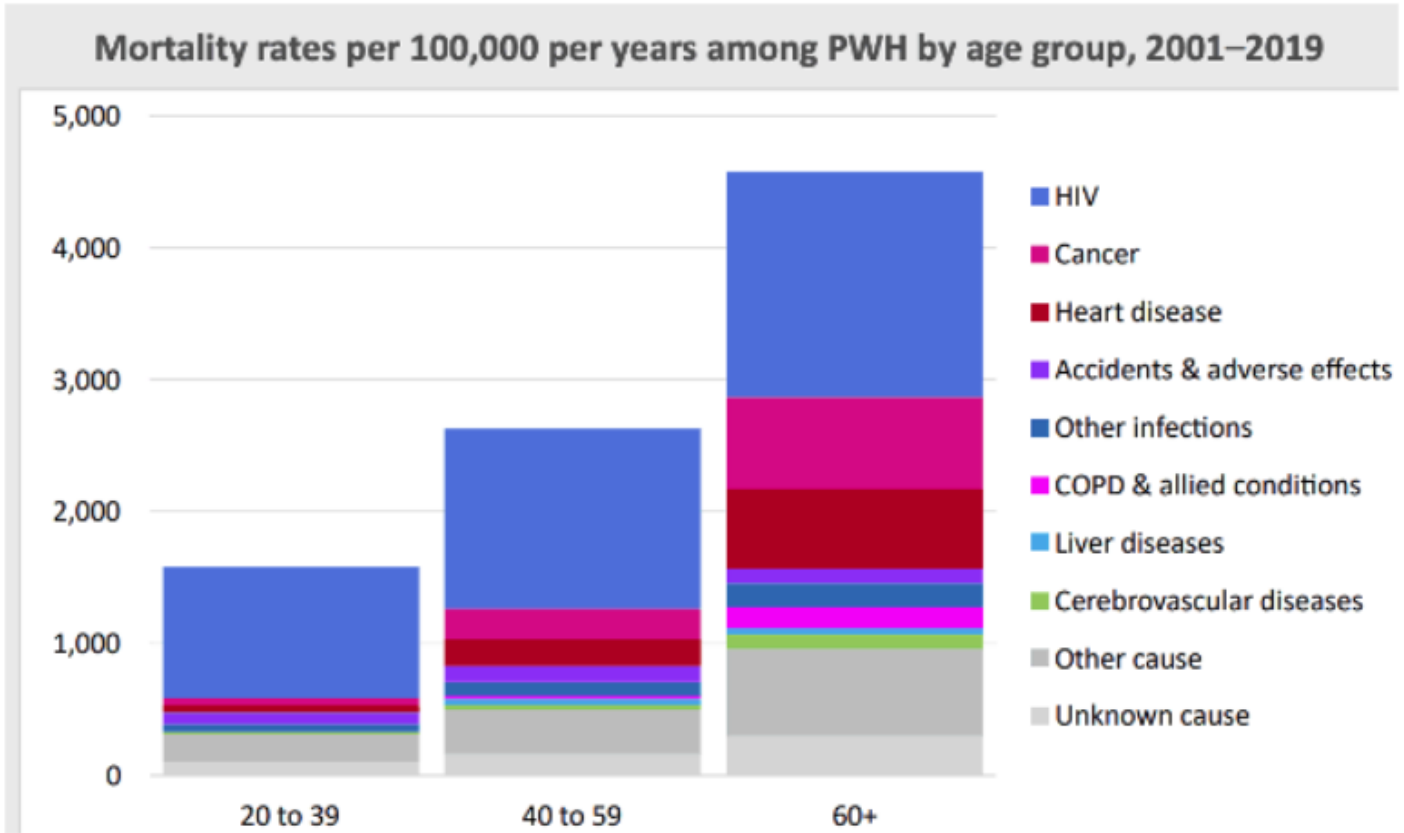


While participants were not allowed to switch CVD risk groups, the proportion of **very high estimated CVD risk** individuals increased in 2019 **(49%)** vs 2012 **(31.5%)**

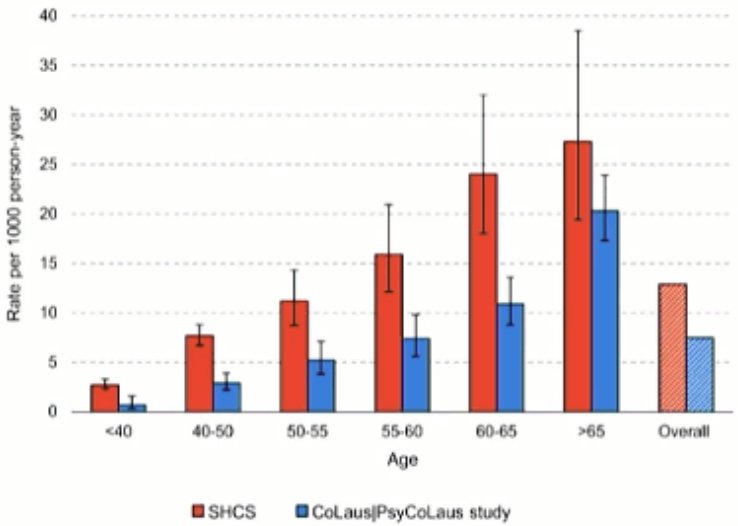
Leading Causes of Death Among People With HIV in the US, 2001-2019...4x greater death risk than gen. pop., cancer & heart disease, HIV leading causes of death, Blacks have higher death rates

CROI 2024 March 3-6 Denver

Karena Volesky-Avellaneda, Eric Engels, Qianlai Luo, Meredith Shiels



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

biomedicines

Article

Evaluation of myo-intimal media thickness and atheromatous plaques in people living with HIV from the Archiprevaleat cohort vs HIV-negative subjects.

Salvatore Martini[1], Elena Delfina Ricci[2], Addolorata Masiello[3], S. Zacà[4], Benedetto Maurizio Celesia[5], Sergio Ferrara[6], Giovanni Di Filippo[7], Alessandra Tartaglia[8], Rosa Basile[9], Domenico Angiletta[4], Paolo Maggi [1,3]

1. Università della Campania Luigi Vanvitelli, Naples, Italy
2. Fondazione ASIA Onlus, Milan, Italy
3. AORN Sant'Anna e San Sebastiano, Caserta, Italy
4. Chirurgia Vascolare ed Endovascolare "Aldo Moro", Università di Bari, Bari Italy
5. Azienda Ospedaliera ARNAS Garibaldi, Catania, Italy
6. Università degli Studi, Foggia, Italy
7. Università Federico II di Napoli, Italy
8. Azienda Ospedaliera Foggia, Italy
9. Grande Ospedale Metropolitano Reggio Calabria, Italy

* Correspondence: salvatoremartini76@gmail.com; Tel: +393283783595

Figure 1. Study design

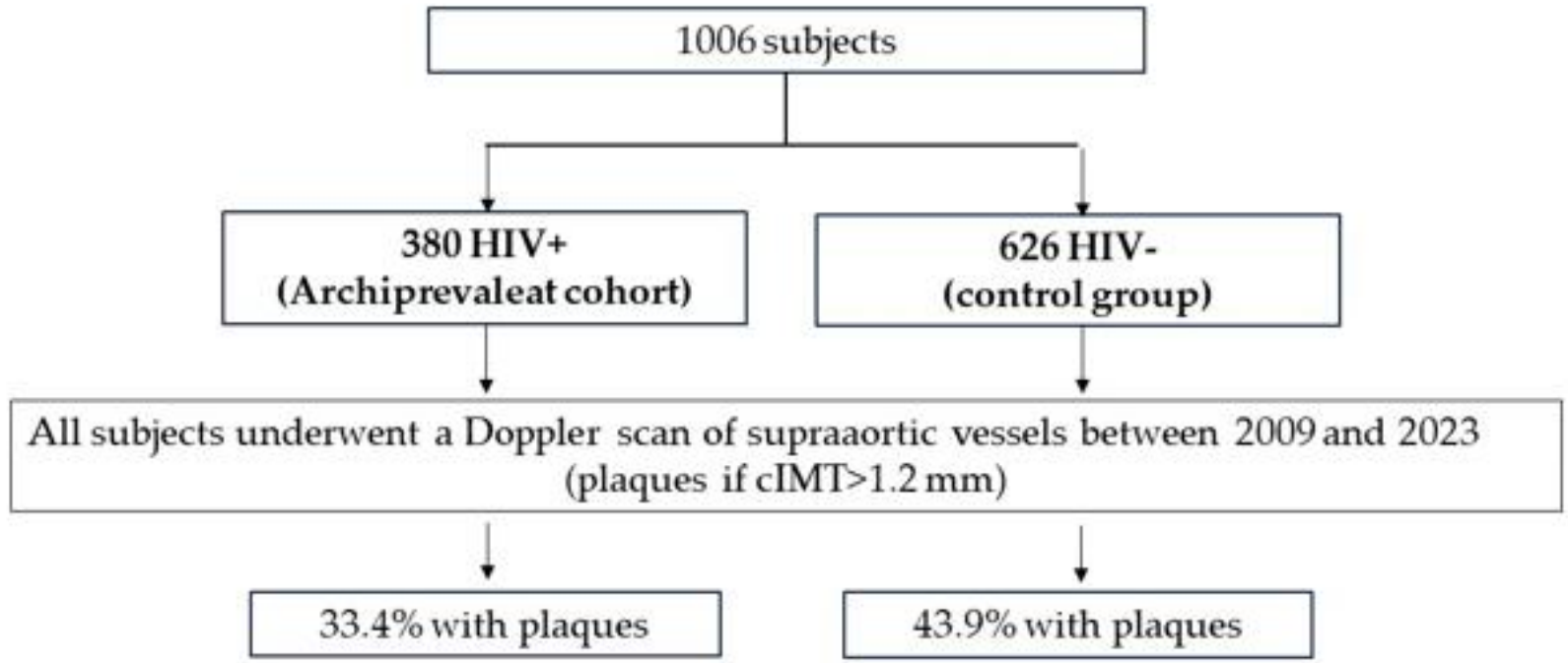


Figure 3. Prevalence of plaques in HIV-positive (n=380) and HIV-negative (n=626) people, total and by age class.

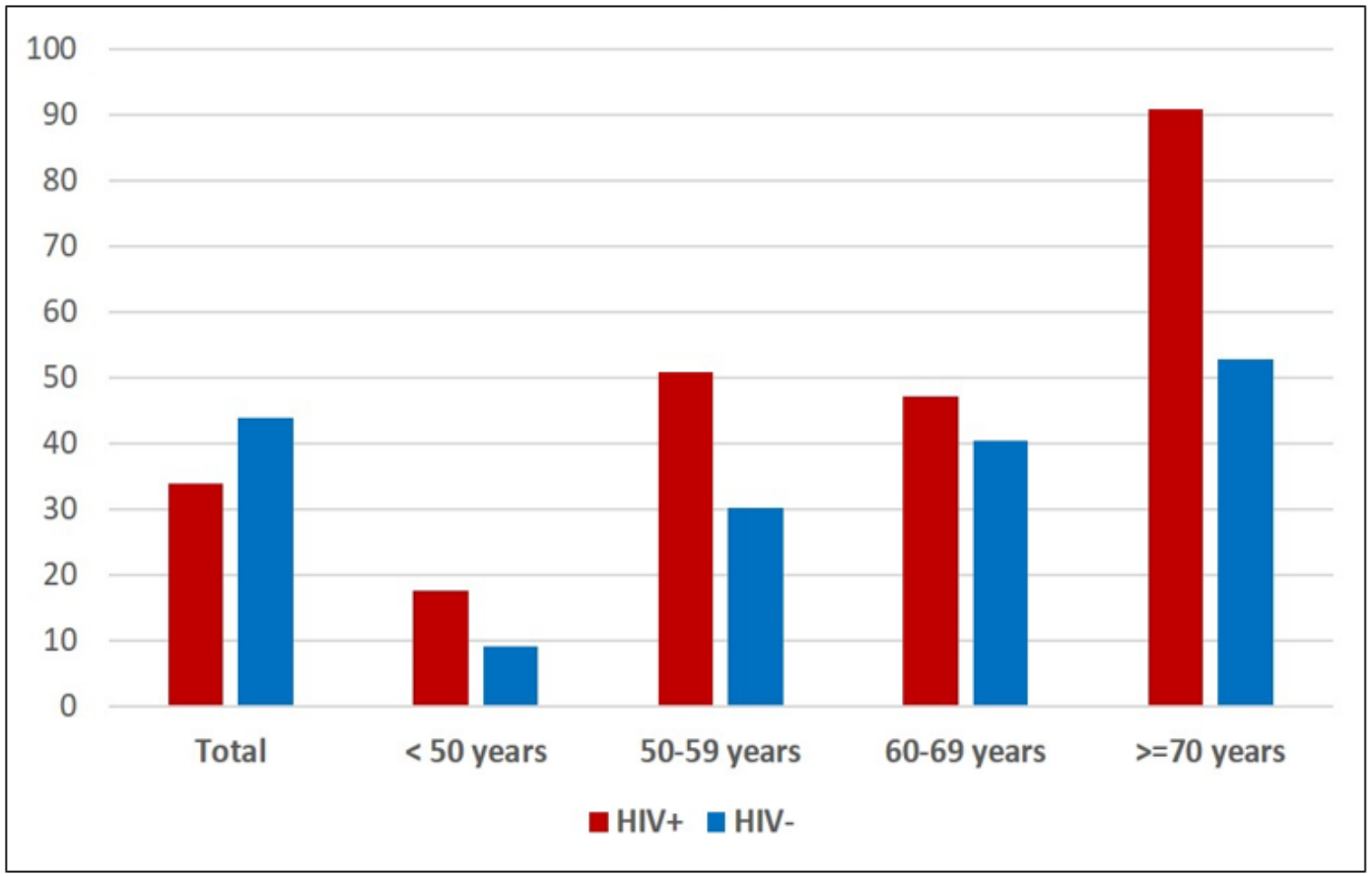


Figure 4. Odds ratios for risk of plaque (IMT >1.2 mm) in HIV-infected patients compared to HIV-negative subjects..

Inflammation:

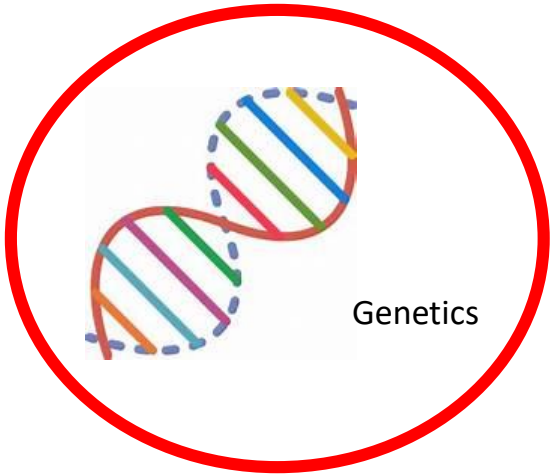
The keystone of aging and chonic diseases

Sedentary lifestyle

Environment pollution

Junk food

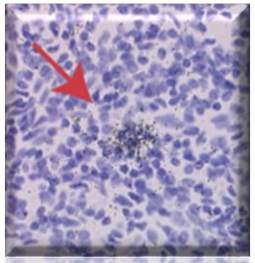
Smoking



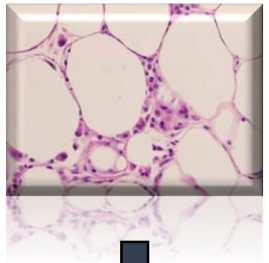
Inflammaging:

a major characteristic of HIV

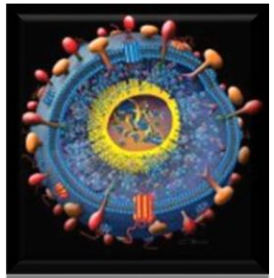
HIV production
HIV replication



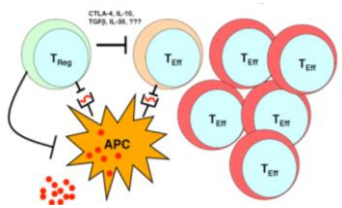
HIV-associated fat
Metabolic syndrome



CMV
Excess pathogens

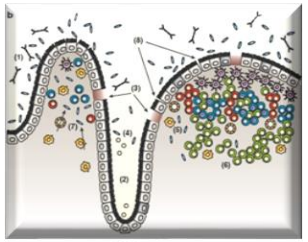


Loss of regulatory cells



Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

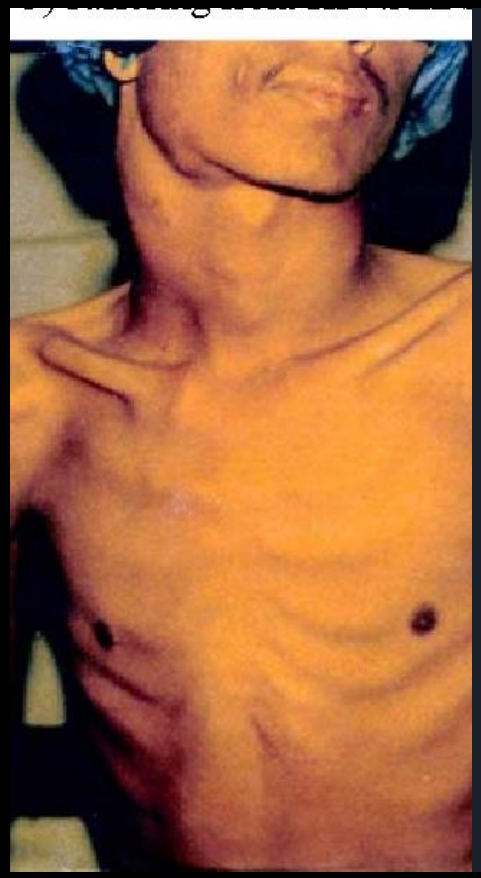
Microbial translocation



Co-morbidities
Aging

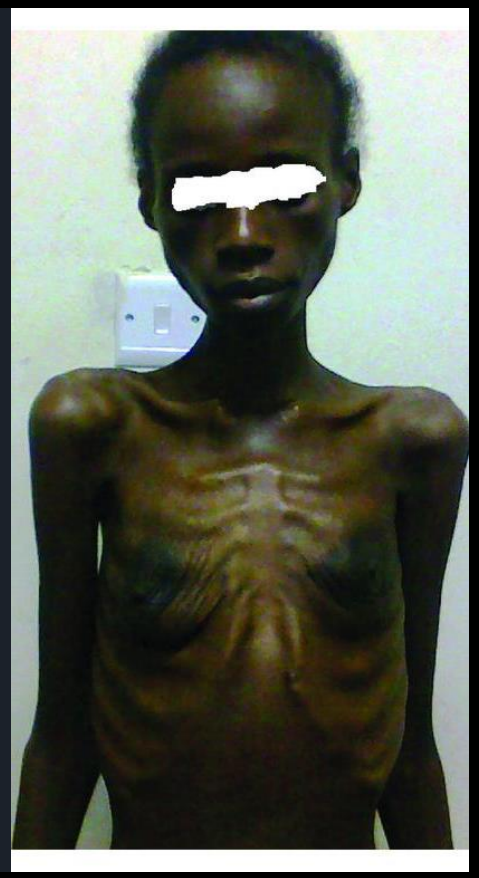
S. Deeks, Lancet 2013

Weight gain:
the third era

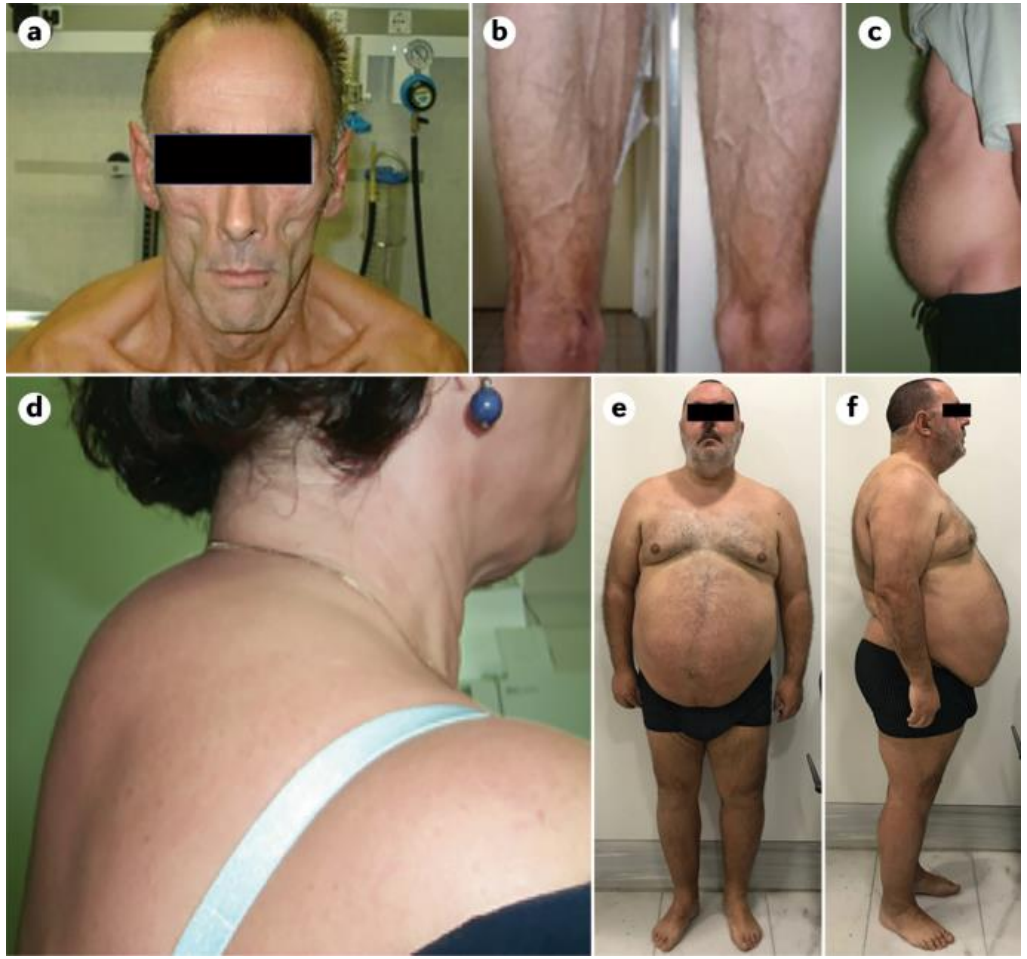


Pre-ART ERA:

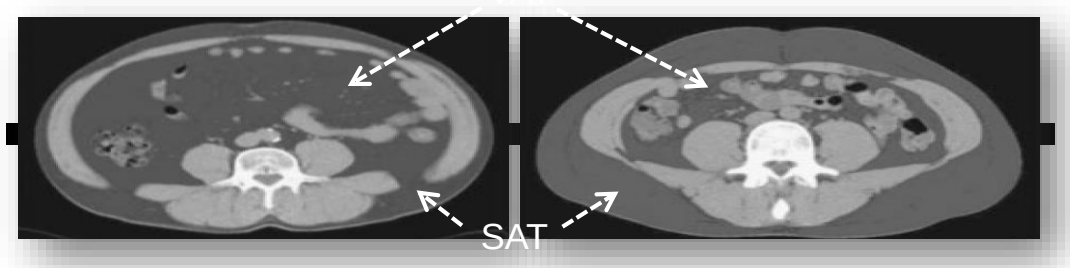
wasting syndrome

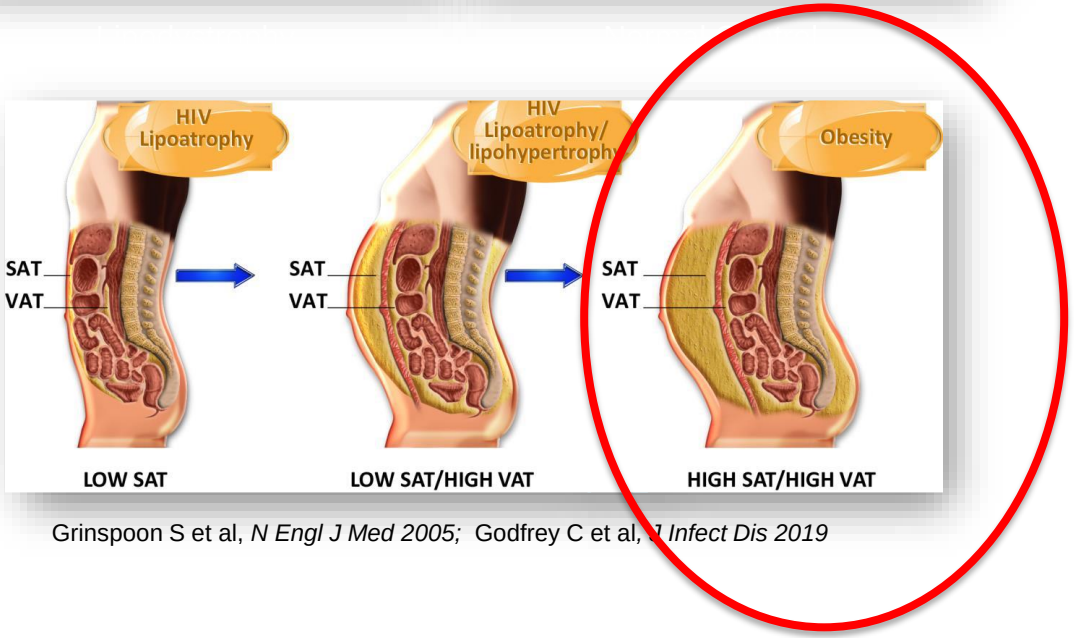


Old and new ARVs



Body-Fat Abnormalities in HIV-Infected Adults

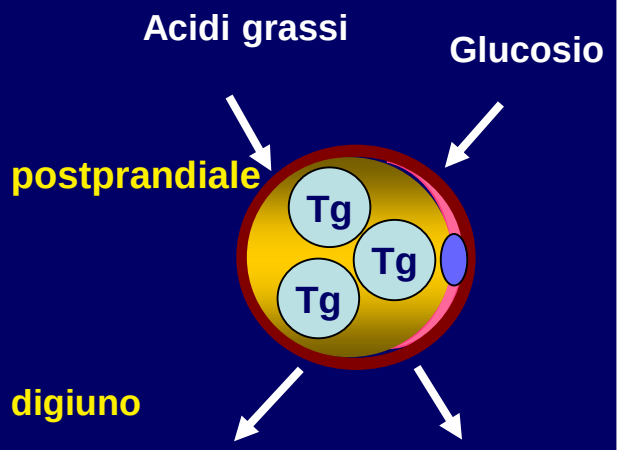




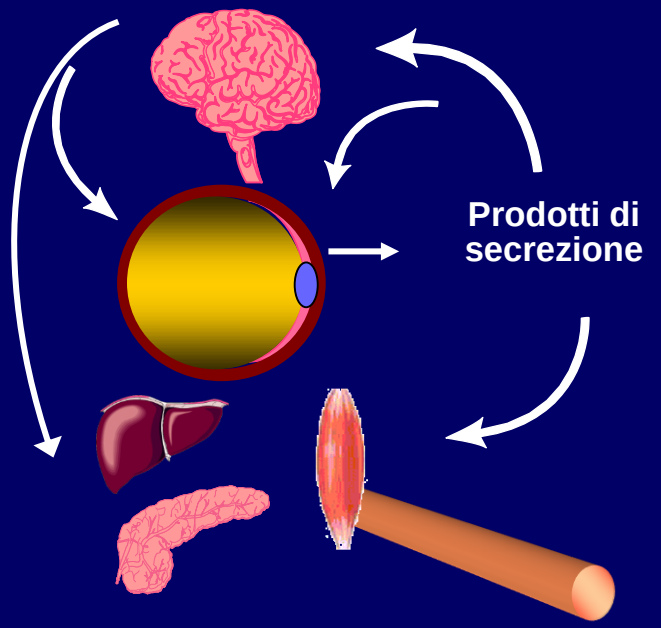
Grinspoon S et al, *N Engl J Med 2005;* Godfrey C et al, *J Infect Dis 2019*

L’evoluzione del concetto di tessuto adiposo: da deposito a organo endocrino

ANTICA VISIONE:
passivo deposito di energia



ATTUALE VISIONE:
organo endocrino



Lyon CJ et al. Endocrinology. 2003;144:2195-2200

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Grinspoon SK et al. DOI: 10.1056/NEJMoa2304146

CLINICAL PROBLEM

In persons with HIV infection, the risk of atherosclerotic cardiovascular disease is twice that in the general population. Randomized studies of primary prevention strategies in this population are needed.

CLINICAL TRIAL

Design: A phase 3, multinational, randomized, placebo-controlled trial assessed the efficacy and safety of pitavastatin for the prevention of cardiovascular events in persons with HIV infection and low-to-moderate risk of atherosclerotic cardiovascular disease.

Intervention: 7769 participants between the ages of 40 and 75 years (median screening LDL cholesterol, 108 mg/dl) receiving stable antiretroviral therapy were assigned to receive oral pitavastatin calcium (4 mg) (3888 participants) or placebo (3881 participants) daily. The primary outcome was the occurrence of a major adverse cardiovascular event — cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause, as measured in a time-to-event analysis.

RESULTS

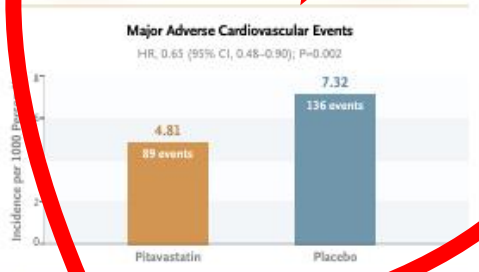
Efficacy: During a median follow-up of 5.1 years, the incidence of major adverse cardiovascular events was significantly lower in the pitavastatin group than in the placebo group.

Safety: The incidence of nonfatal serious adverse events was similar in the two groups. Participants in the pitavastatin group were more likely than those in the placebo group to have newly diagnosed diabetes mellitus and grade ≥3 myalgia, muscle weakness, or myopathy.

LIMITATIONS AND REMAINING QUESTIONS

- Although other statins that do not interact with HIV medications may have similar protective effects, the results reported are specific to pitavastatin.
- Other strategies that lower LDL cholesterol may be useful in this population and need to be compared with statin therapy with respect to efficacy, safety, and cost.

Links: Full Article | NEJM Quick Take | Editorial



CONCLUSIONS

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

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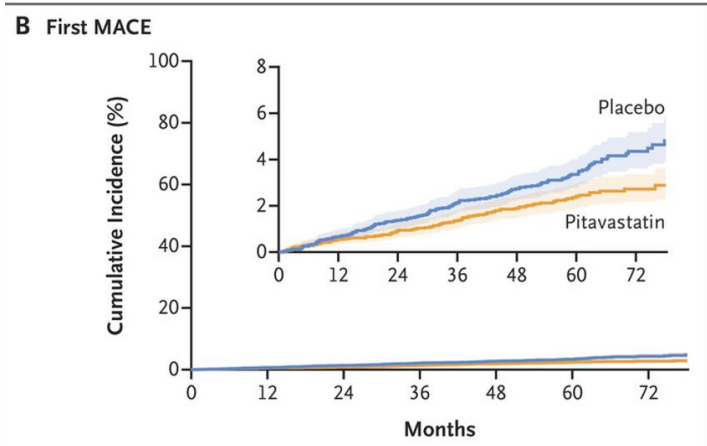
REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV



Cumulative Incidence of Event (%)							
Placebo	0.00	0.66	1.38	2.14	2.74	3.36	4.36
Pitavastatin	0.00	0.56	0.95	1.35	1.89	2.41	2.73

Cumulative Incidence of Event (%)							
Placebo	0.00	0.80	2.03	3.34	4.44	5.35	7.06
Pitavastatin	0.00	0.77	1.58	2.39	3.40	4.54	5.54

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

Statement released: February 27, 2024

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).

Rationale for The Panel's Recommendations for People with HIV Who Are Ages <40 Years at Low-to-Intermediate (<20%) 10-year ASCVD Risk

REPRIEVE did not enroll people with HIV under 40 years of age. In the general population, lifestyle modifications targeting traditional risk factors (e.g., diet, exercise, smoking cessation, and blood pressure control) are recommended for people under 40 years of age.[15] Still, some of these individuals also may benefit from statin therapy, and recommendations for the general population suggest risk factors such as familial hypercholesterolemia or family history of premature ASCVD may favor statin therapy. There are insufficient data to inform whether risk enhancers, such as HIV-related factors, would favor statin therapy among people under 40 years of age. However, some younger people with HIV may be at increased ASCVD risk—particularly those with a very long duration of HIV infection (e.g., due to perinatal exposure). Decisions on statin therapy should be individualized among this population.

Rationale for Recommendations on Statin Therapy for People with HIV Who Are Ages 40 to 75 Years at High (≥20%) 10-year ASCVD Risk or Ages 20 to 75 Years with LDL-C ≥190 mg/dL

The 2018 ACC/AHA/Multisociety Guidelines recommends the use of statins as primary prevention for all people at high risk, defined as ages 40 to 75 years with a 10-year ASCVD risk estimate of ≥20%, as well as those ages 20 to 75 years with an LDL-C ≥190 mg/dL.[15] In this context, an LDL-C reduction of ≥50% should be achieved, which will typically require high-intensity statin therapy (see the Intensity of Statin Therapy table below).

Rationale for Recommendations on Statin Therapy for People with HIV Who Are Ages 40 to 75 Years with Diabetes Mellitus

The 2018 ACC/AHA/Multisociety Guidelines recommends that for people with diabetes mellitus, at least a moderate-intensity statin is recommended with additional risk assessment to inform consideration of initiating a high-intensity statin. These general population guidelines are based on high-quality randomized trial data and should inform the management of people with HIV who meet these criteria.[15]

CLINICAL INFO
HIV.gov

2024
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EUROPA
16° CONGRESSO NAZIONALE
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Italian Conference on AIDS and Antiviral Research
Presidenza del Congresso
A. Cingolani, A. Di Biagio,
M. Farinella, G. C. Marchetti
Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali
RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY

Dyslipidemia and real-life prescription of statins among People Living With HIV enrolled in Archi-Prevaleat cohort.

B. M. Celesia1, S. Martini 2, E. D. Ricci 3, L. Galli 4, A. Masiello 5, C. Muccini 4, S. Zacà 6, S. Ferrara 7, G. Di Filippo 8, M.S. Paternò Raddusa 1, A. Tartaglia 9, R. Basile10, D. Angiletta 6, A. Castagna 4, P. Maggi 2,5.

1 Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, ARNAS Garibaldi Hospital, University of Catania, 95123 Catania, Italy. 2 Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania, Luigi Vanvitelli, 80131 Naples, Italy 3 Fondazione ASIA Onlus, 20090 Milan, Italy, 4 Clinic of Infectious Diseases, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy. 5 AORN Sant'Anna e San Sebastiano of Caserta, 81100 Caserta, Italy. 6 Department of Emergency and Organ Transplantation, University of Bari School of Medicine, 70121 Bari, Italy. 7 Department of Medical and Surgical Sciences, Section of Infectious Diseases, University of Studies of Foggia, 71122 Foggia, Italy. 8 Department of Medicine and Surgery, Section of Infectious Diseases, University Federico II of Naples, 80138 Napoli, Italy. 9 Azienda Ospedaliera di Foggia, 35128 Foggia, Italy. 10 Section of Infectious Diseases, Grande Ospedale Metropolitano, Bianchi Melacrino Morelli, 89124 Reggio Calabria, Italy

Statins should be used by all those with established vascular disease and in persons who are not at LDL-c goals considering their level of CVD risk, irrespective of lipid levels, see Treatment Goals for LDL-c to reduce cardiovascular risk depending on CV risk estimation.

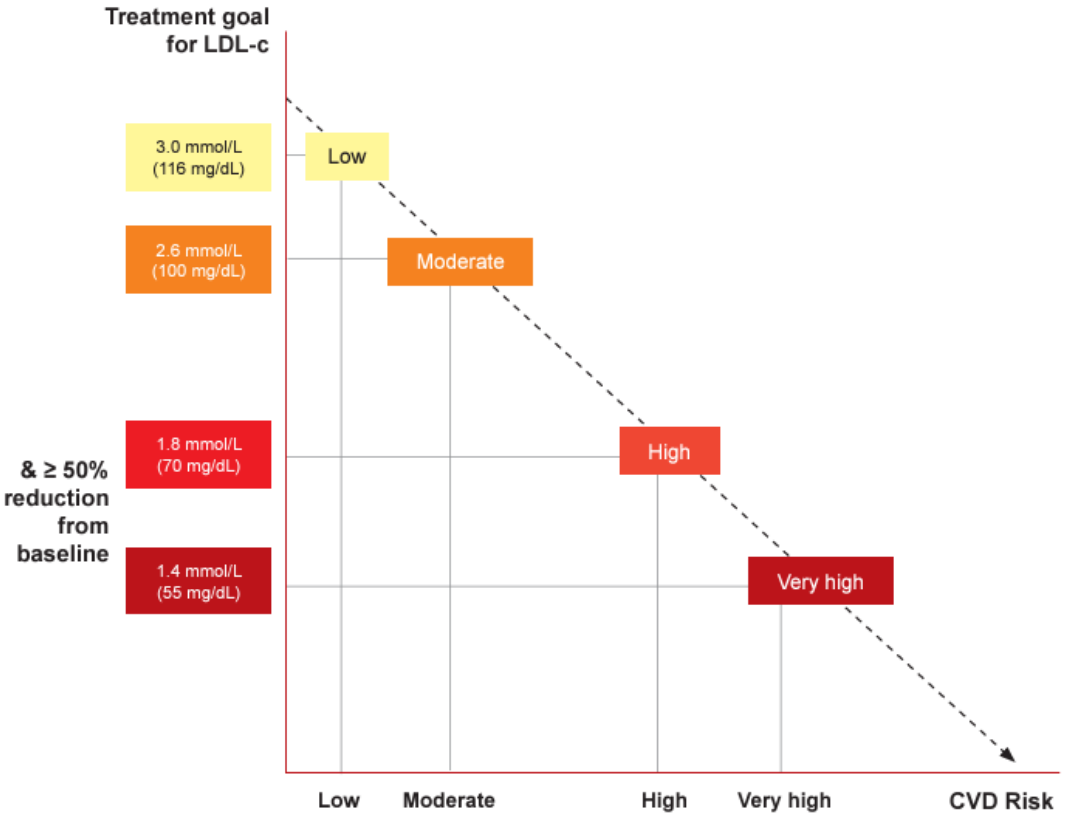
In high risk persons with statin intolerance, drug-drug interactions between high intensity statins and ART, or those unable to reach LDL-c goals on statins and/or ezetimibe, a PCSK9 inhibitor and/or bempedoic acid should be considered. Icosapent ethyl (EPA) should be discussed in adjunct to statin in very high risk patients (post MI and diabetics with another CV risk factor with TGs > 150mg/dL or > 1.7 mmol/L.

SCORE2 and SCORE2-OP Cardiovascular disease risk estimation stratified by age*

CV risk estimation	< 50y	50-69y	> 70y
Low / moderate	< 2.5%	< 5%	< 7.5%
High	2.5-<7.5%	5-<10%	7.5-<15%
Very high	> 7.5%	> 10%	> 15%

* For the cardiovascular risk definitions, please refer to the 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk.

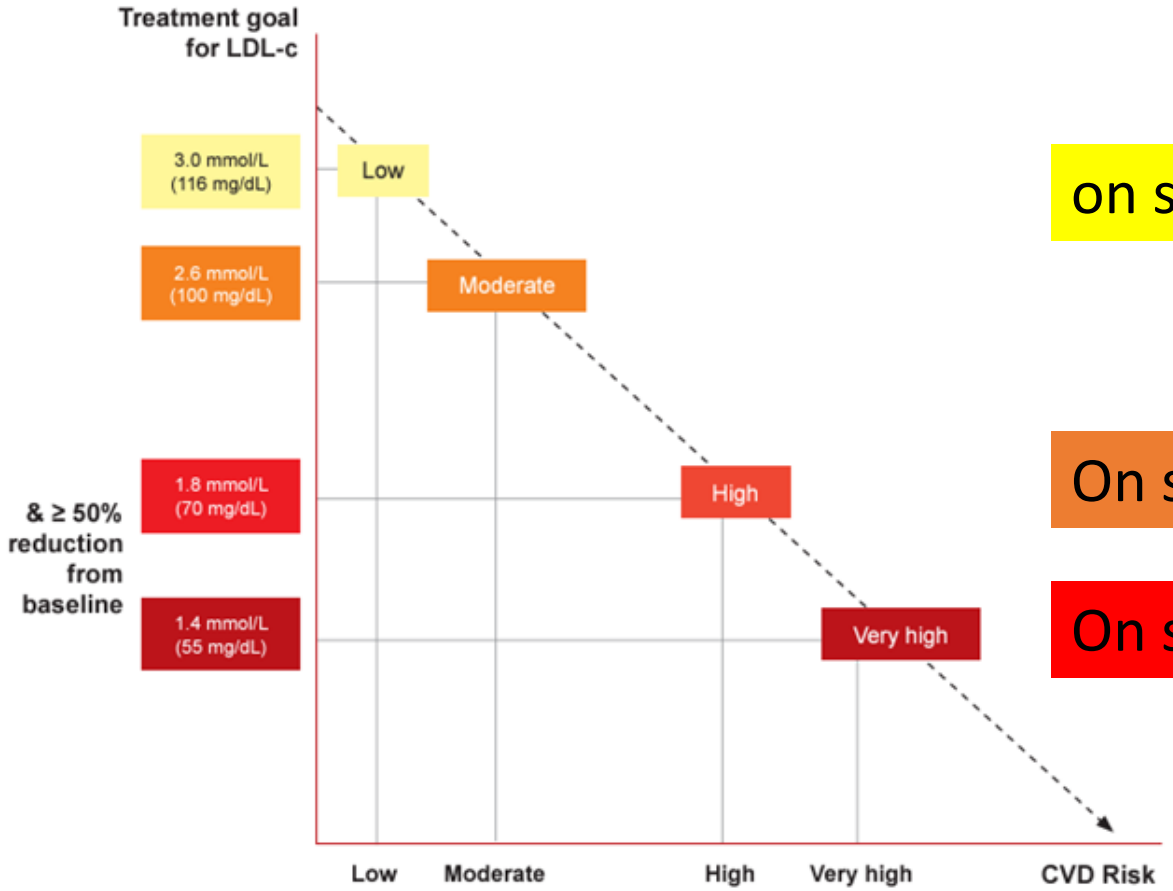
Treatment Goals for LDL-c to Reduce Cardiovascular Risk Depending on CV Risk Estimation*



Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering*
Adapted from: 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188.

results

Treatment Goals for LDL-c to Reduce Cardiovascular Risk Depending on CV Risk Estimation*



on statin 28 (23,3%)

On statin 91 (33,7%)

On statin 143 (36,3%)

Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering*
Adapted from: 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188.

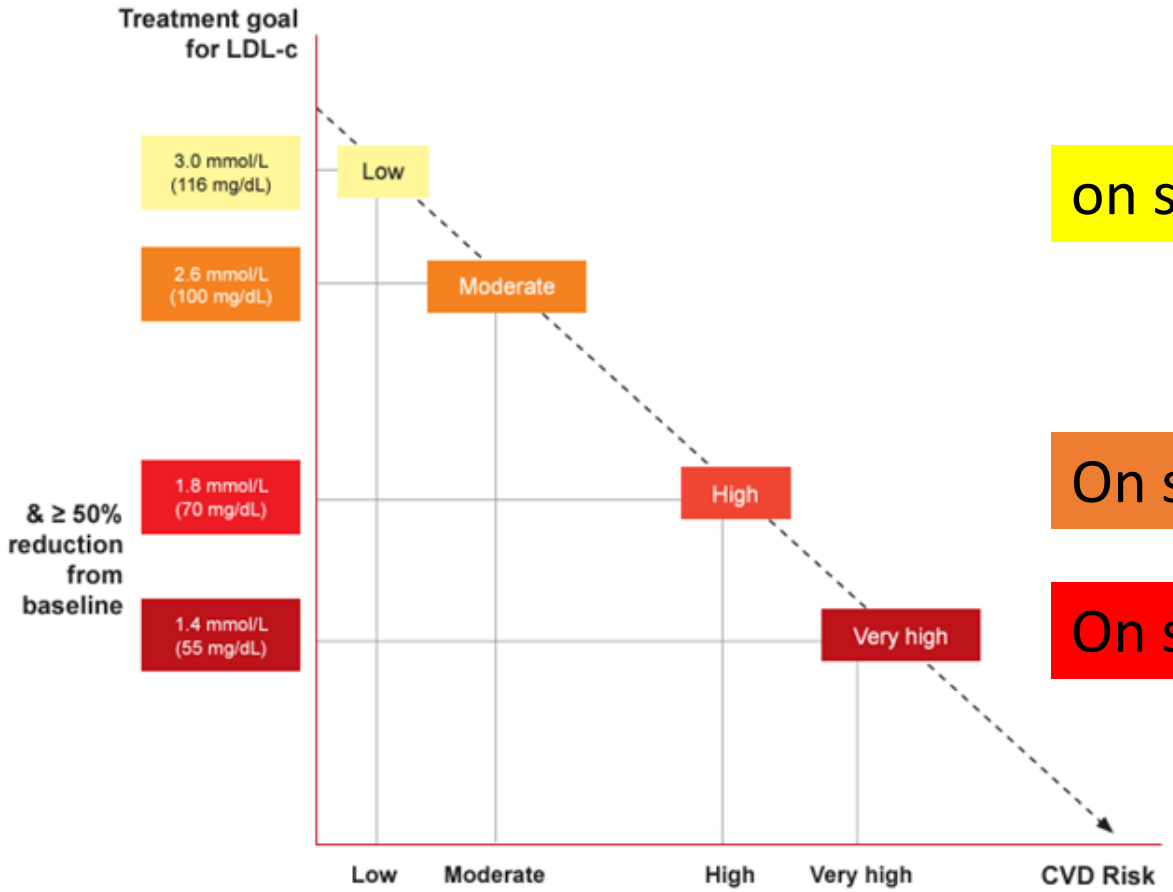
results

on target 55 (45,8%)

on target 13 (3,9%)

on target 9 (2,2%)

Treatment Goals for LDL-c to Reduce Cardiovascular Risk Depending on CV Risk Estimation*



Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering*
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on statin 28 (23,3%)

On statin 91 (33,7%)

On statin 143 (36,3%)

results

Globally, any thickness or plaques were detected in 553 (36.6%) subjects.

211 out of 372 (56,7%) PLWH with high CVD risk showed any IMT or plaque;
87 (41.7%) of them were on treatment with statins.

189 subjects among 372 (50,8%) at high CVD risk showed any IMT or plaque associated with LDLc value >70 mg/dl.
74 (37%) of them were on treatment with statins.

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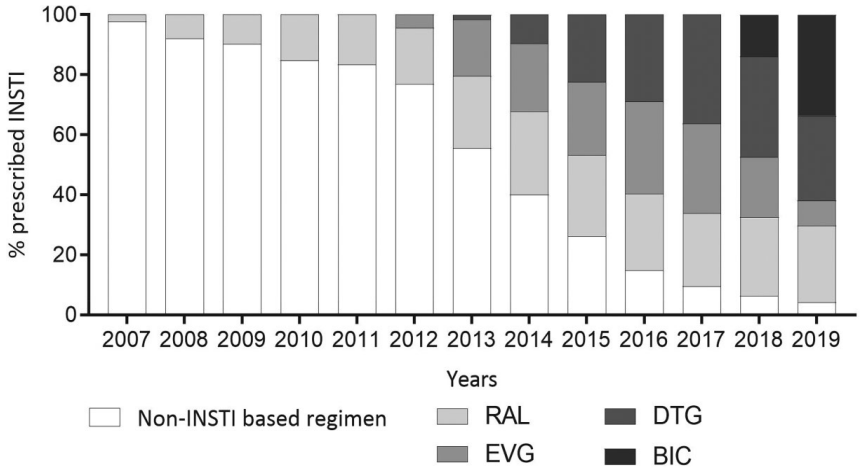
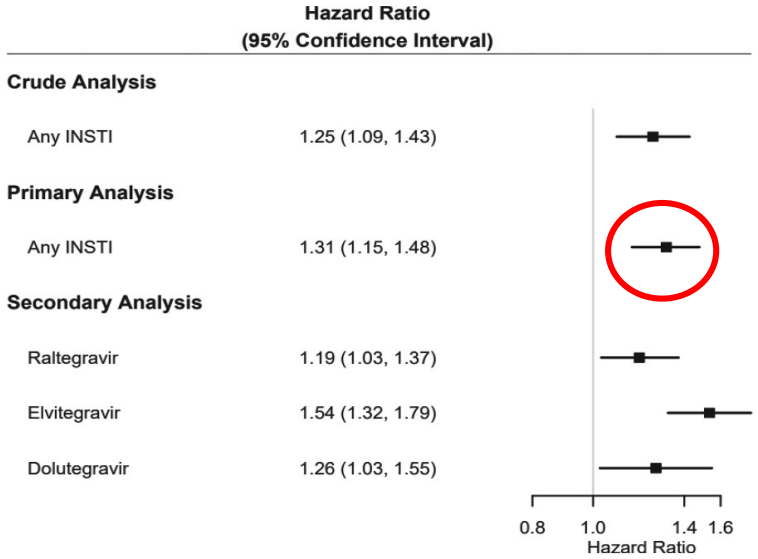
Integrase Strand Transfer Inhibitors Are Associated With **Incident Diabetes Mellitus** in PWHIV

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.

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

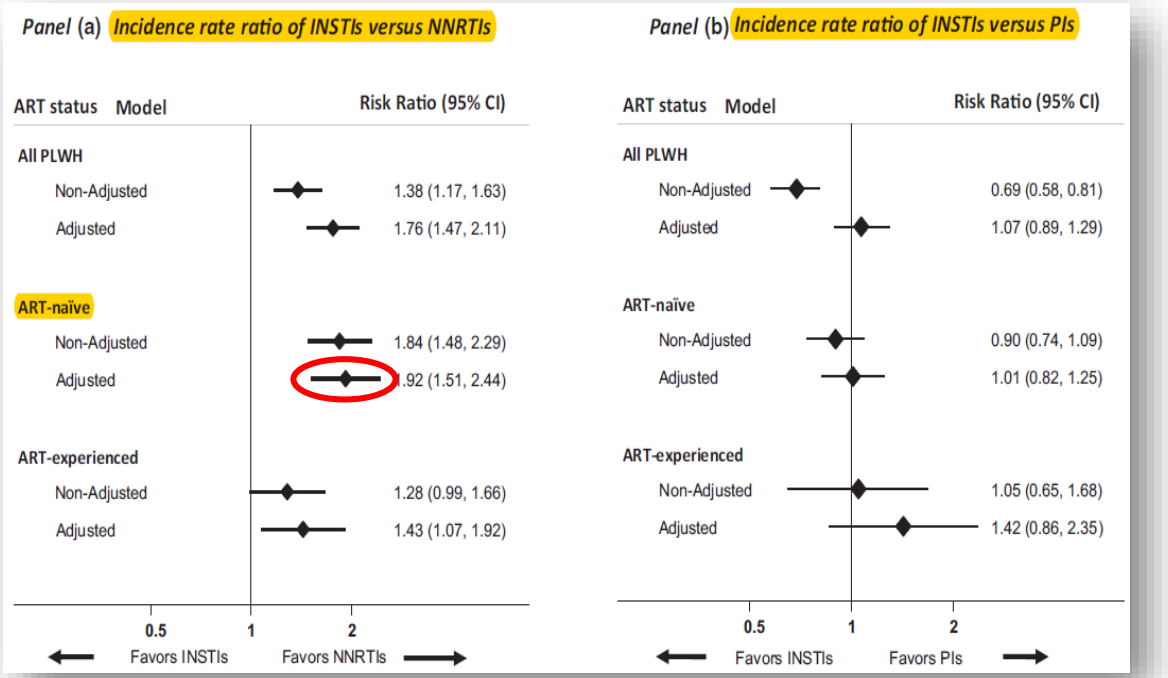
Variation in BG are not significantly different in PLWH starting for the first time BIC vs DTG therapy at a follow-up of 12 months. To be Naïve or Experienced to Antiretroviral treatment does not have a significant impact on BG variation in this cohort.

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

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.

1. Bansi-Matharu. Lancet HIV 2021; 8: e711–22 2. Byonaneby et al. AIDS 2021, 35:869–882 3. Byonaneby at al. HIV Medicine. 2022;23:895–910. 4. O'Halloran et al https://doi.org/10.1093/cid/ciac355
5. Bischoff et al. EClinicalMedicine 40 (2021) 101116 6. Neesgaard et al. Lancet HIV 2022; 9: e474–85 7. Rebeiro PF, AIDS 2022 EPB108

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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1 Strong C, Huang P, Li C-W, Ku SW-W, Wu H-J, Bourne A. HIV, chemsex, and the need for harm-reduction interventions to support gay, bisexual, and other men who have sex with men. *Lancet HIV* 2022; **9**: e271–75.
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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	1127	121 696	1 (ref)	..	..
Previous TDF 1 year+ PDC <80%	78	8497	0·89	0·75–1·13	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.[1] 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]

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1 Neesgaard B, Greenberg L, Miró JM, et al. Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium. *Lancet HIV* 2022; **9**: e470–85.
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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' 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.[1] 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,[4] 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.[1,5]

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.

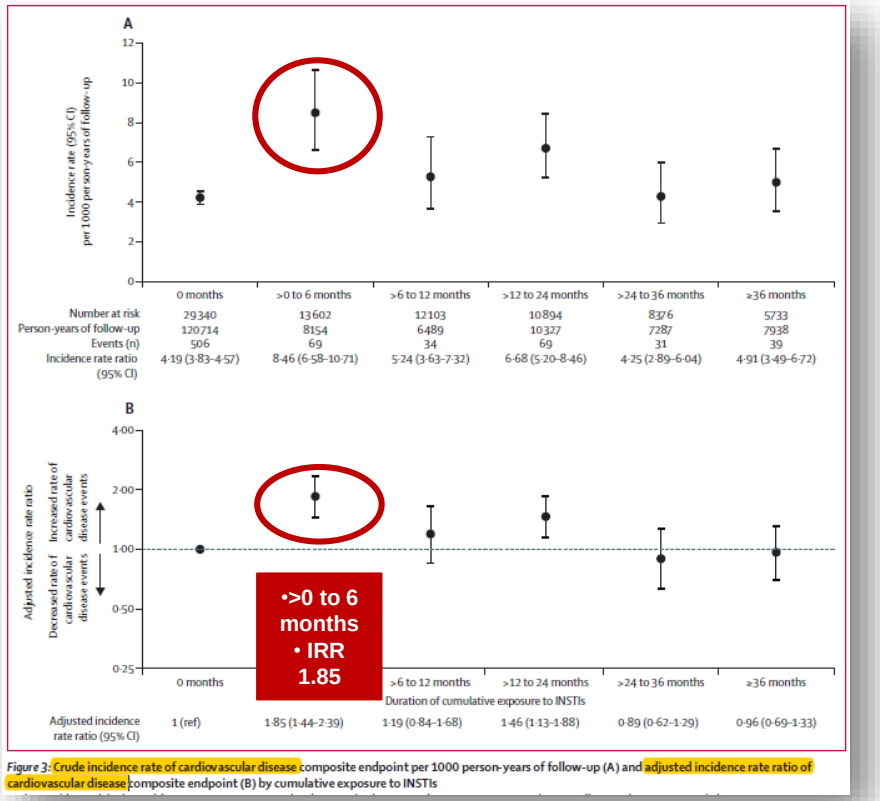

Figure 3: Crude incidence rate of cardiovascular disease composite endpoint per 1000 person-years of follow-up (A) and adjusted incidence rate ratio of cardiovascular disease composite endpoint (B) by cumulative exposure to INSTIs

Neesgaard B et al_Lancet HIV 2022

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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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

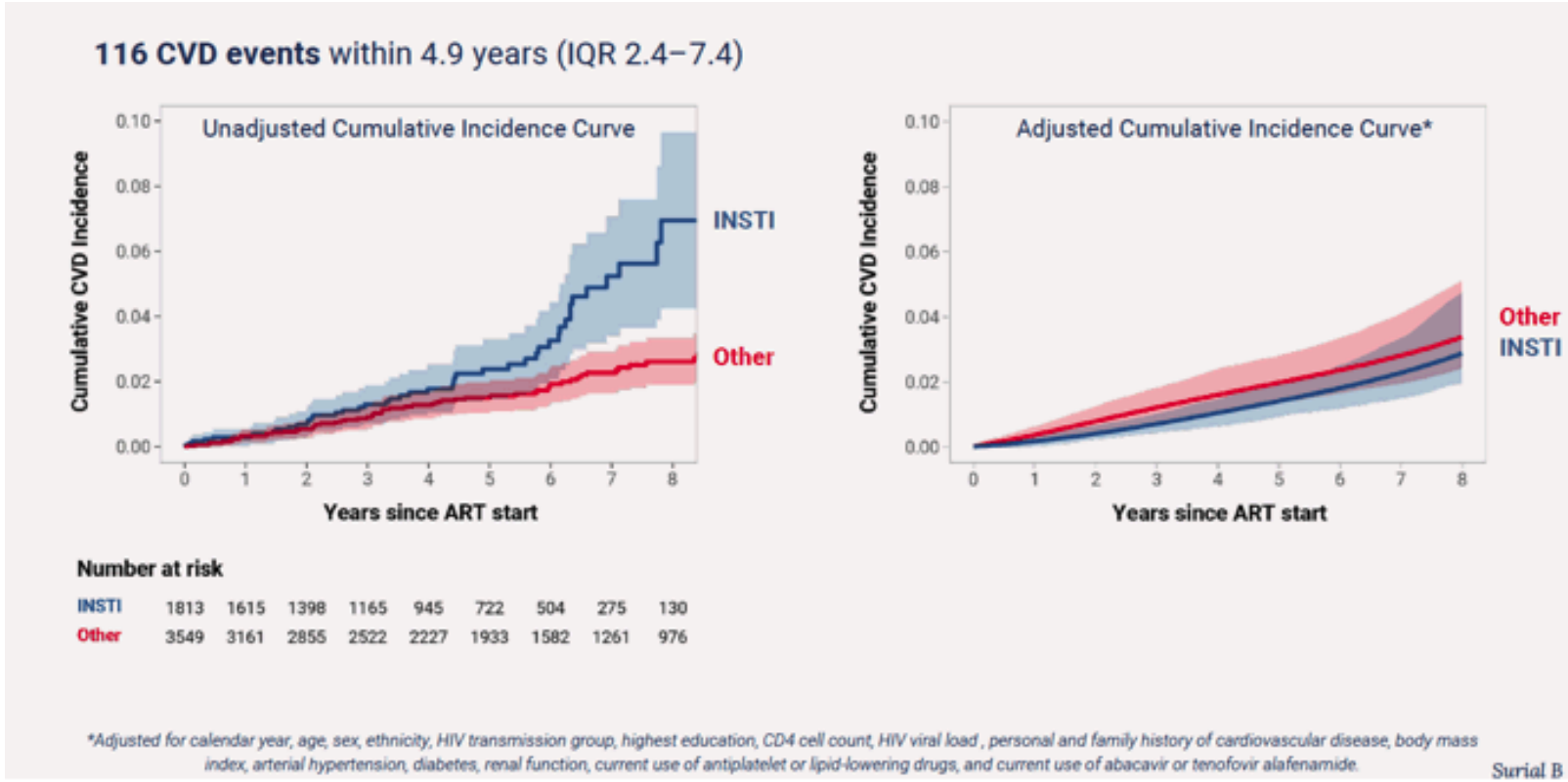
Table 2. Details of ARV treatment in 1147 HIV-positive patients included in the baseline analysis, according to the presence of plaques.

	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** ▾



*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.

viruses

MDPI

Article

Risk of Cardiovascular Events in People with HIV (PWH) Treated with Integrase Strand-Transfer Inhibitors: The Debate Is Not Over; Results of the SCOLTA Study

Nicolò Corti [1,2], Barbara Menzaghi [3], Giancarlo Orofino [4], Marta Guastavigna [4], Filippo Lagi [5], Antonio Di Biagio [6,7], Lucia Taramasso [6], Giuseppe Vittorio De Socio [8], Chiara Molteni [9], Giordano Madeddu [10], Elena Salomoni [11], Giovanni Francesco Pellicanò [12], Emanuele Pontali [13], Rita Bellagamba [14], Benedetto Maurizio Celesia [15], Antonio Cascio [16], Eleonora Sarchi [17], Roberto Gulminetti [18], Leonardo Calza [19], Paolo Maggi [20], Giovanni Cenderello [21], Alessandra Bandera [22], Maria Aurora Carleo [23], Katia Falasca [24], Sergio Ferrara [25], Salvatore Martini [26], Giuliana Guadagnino [27], Goffredo Angioni [28], Olivia Bargiacchi [29], Elena Delfina Ricci [30,*], Nicola Squillace [1] and Paolo Bonfanti [1,2]

- Among 2357 PWH exposed to INSTIs, 24 people experienced CVD; the corresponding figure was 12 cases out of 2599 PWH exposed to other ART classes. At univariate and multivariate analysis, a tendency towards an increased risk of CVD was observed in the 2-year follow-up period in PWH exposed to INSTIs in the absence, however, of statistical significance.
- These findings leave open the hypothesis that INSTIs may play a role, albeit minimal, in determining an increased risk of CVD in PWH.

Viruses 2024, 16, 613. https://doi.org/10.3390/v16040613

Table 2. Incidence rates and rate ratios of first CV events (2-year and complete follow-up).

	N	Events	PYFU	Crude IR/1000 PYFU (95% CI)	Crude RR (95% CI)	Adjusted * IR/1000 PYFU (95% CI)	Adjusted * RR (95% CI)
2-year follow-up							
Total	4984	28	7321.37	3.8 (2.6–5.5)		6.7 (3.6–12.2)	
INSTI	2192	19	3736.59	5.1 (3.2–8.0)	2.02 (0.91–4.46)	8.7 (4.5–16.7)	1.55 (0.67–3.56)
Non INSTI	2792	9	3574.54	2.5 (1.3–4.8)		5.6 (2.4–12.8)	
Naïve	1020	4	1459.94	2.7 (1.0–7.3)	0.67 (0.23–1.93)	6.2 (2.0–19.0)	0.82 (0.28–2.39)
Experienced	3964	24	5851.18	4.1 (2.7–6.1)		7.6 (4.1–14.0)	
Complete follow-up							
Total	4984	36	11,688.51	3.1 (2.2–4.3)		7.4 (4.1–14.5)	
INSTI	2356	24	6770.75	3.5 (2.4–5.3)	1.45 (0.72–2.90)	5.4 (2.9–10.0)	1.10 (0.53–2.29)
Non INSTI	2598	12	4907.51	2.4 (1.4–4.3)		4.9 (2.3–10.5)	
Naïve	1020	5	2149.58	2.3 (1.0–5.6)	0.72 (0.28–1.84)	4.8 (1.7–13.3)	0.91 (0.35–2.36)
Experienced	3934	31	9528.67	3.2 (2.3–4.6)		5.3 (3.0–9.4)	

* Including age ≥ 50 years, diabetes (Y/N), smoking habits (never, former, and current smokers; a class was added for missing information on smoking, since this data was missing in about one third of the sample). CI: confidence interval; INSTI: integrase strand transfer inhibitors; IR: incidence rate; PYFU: person year follow-up; RR: rate ratio.

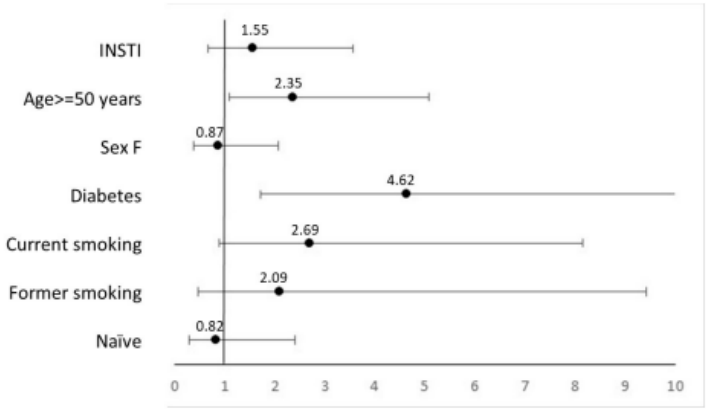


Figure 2. Adjusted rate ratios for cardiovascular events (2-year follow-up).

In summary, our research suggested that an increase in CV risk may occur during INSTI exposure, particularly in the initial two years of treatment. Nevertheless, the lack of statistical significance prevents us from drawing any conclusions.

The need of further research is compelling because, even if the recent findings do not tarnish the excellent pharmacological features of INSTIs, they raise the issue whether INSTIs may increase CV risk in certain people.

It is essential to individualize risk assessments for each patient and incorporate CV risk factors evaluations into follow-up appointments, implementing strategies to mitigate these risks.

Early intervention and tailored care may ensure the benefits of INSTIs outweigh their potential risks. As new treatment options become available, the medical community can refine its approach, providing PWH with the most effective and safe treatment regimen, ultimately promoting personalized medicine for a healthier future and improved quality of life

Viruses 2024, 16, 613. https://doi.org/10.3390/v16040613

NNRTIs and CV safety

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

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: othe. 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

Paolo Maggi[1], Elena Delfina Ricci[2*], Stefania Cicalini[3], Giovanni Francesco Pellicanò[4], Benedetto Maurizio Celesia[5], Francesca Vichi[6], Antonio Cascio[7], Eleonora Sarchi[8], Giancarlo Orofino[9], Nicola Squillace[10], Giordano Madeddu[11], Giuseppe Vittorio De Socio[12], Olivia Bargiacchi[13], Chiara Molteni[14], Addolorata Masiello[1], Annalisa Saracino[15], Barbara Menzaghi[16], Katia Falasca[17], Lucia Taramasso[18], Antonio Di Biagio[18] and Paolo Bonfanti[19]

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.

Lipids, weight gain and Body Mass Index in ARV experienced PLWH treated with Doravirine-based treatments: a comparison between dual or triple regimens vs Bictegravir based triple regimen.

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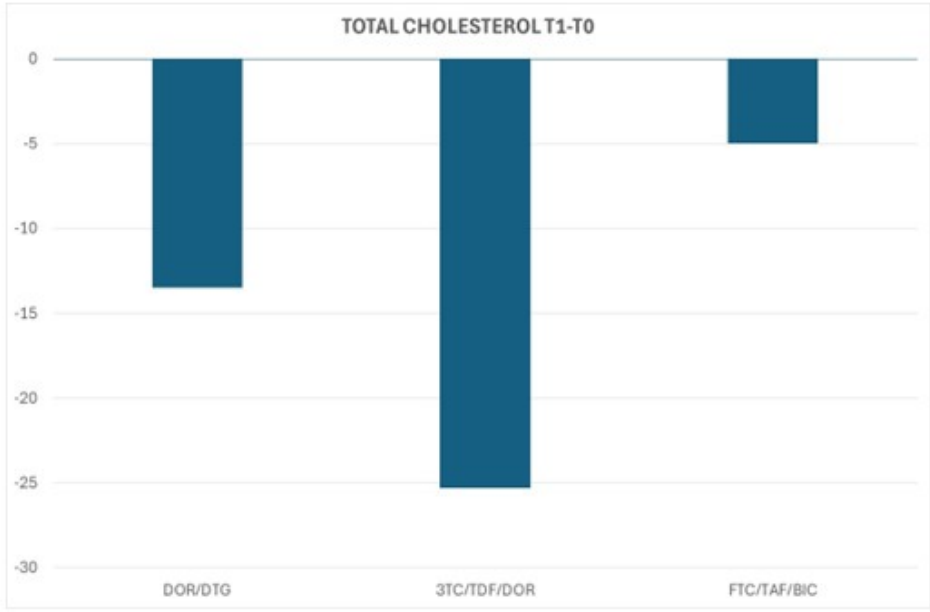
PROGETTO SCOLTA HIV

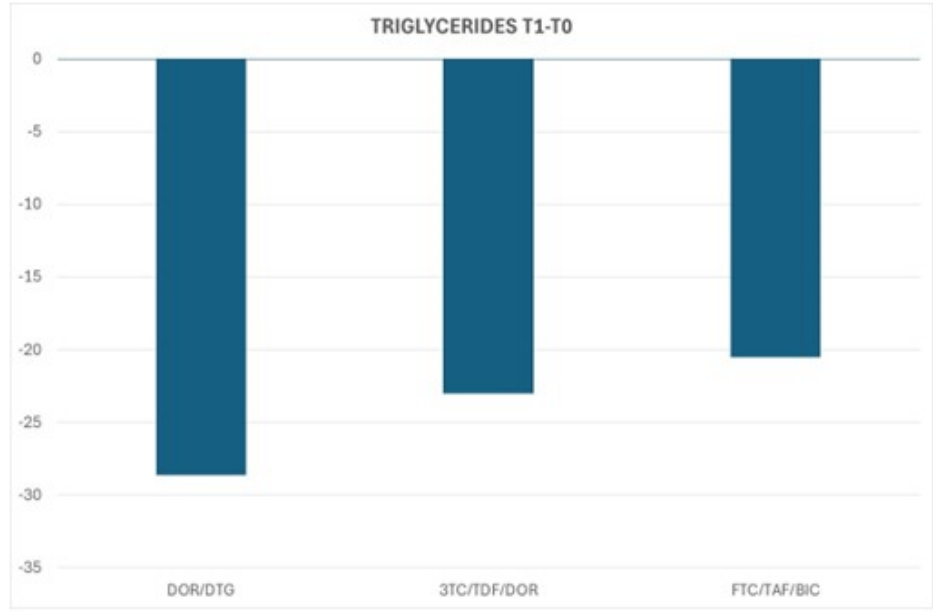
Lipids, weight gain and Body Mass Index in ARV experienced PLWH treated with Doravirine-based treatments: a comparison between dual or triple regimens vs Bictegravir based triple regimen.

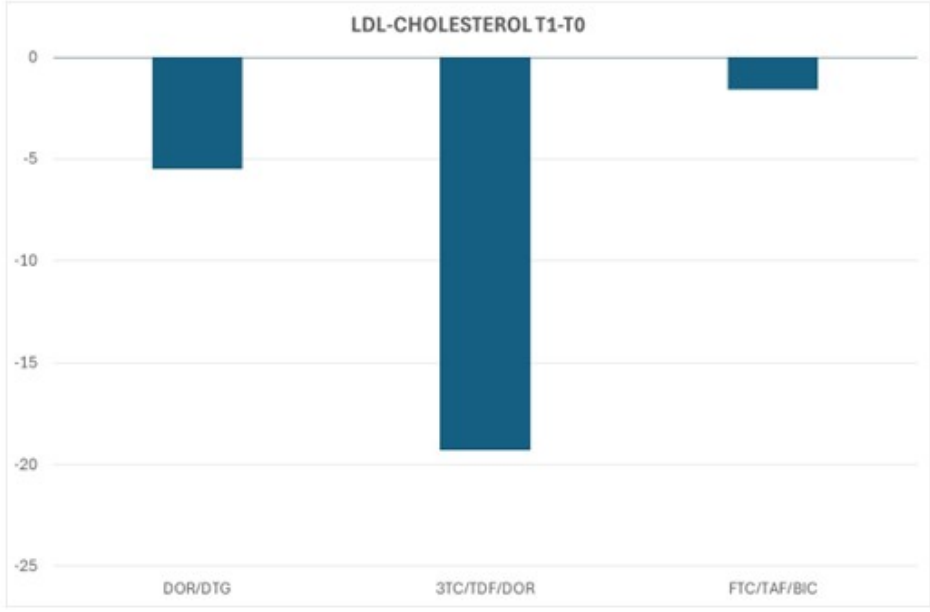
Table 1. Baseline characteristics of 392 PLWH enrolled in the SCOLTA cohorts.

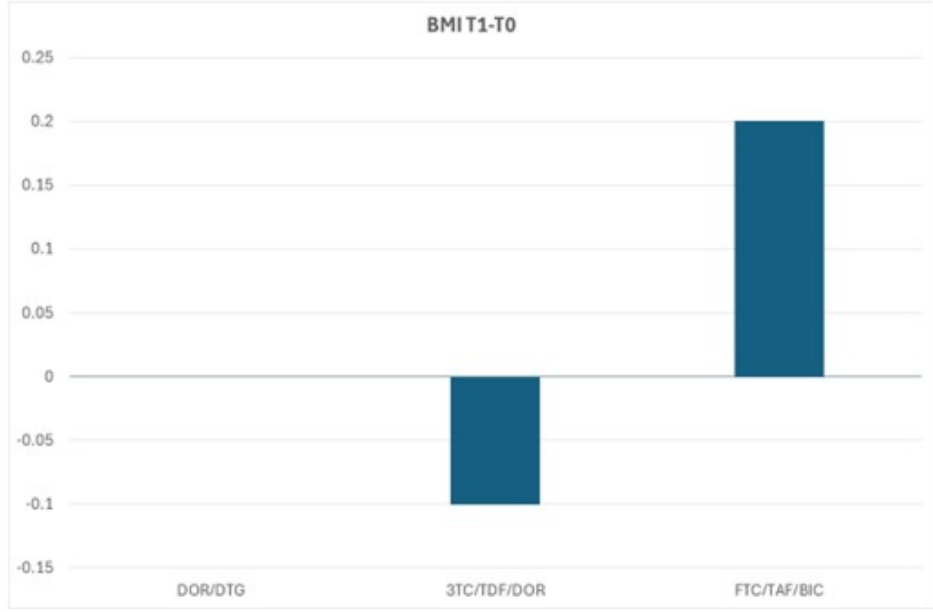
	DOR/DTG N=64		3TC/TDF/DOR N=164		FTC/TAF/BIC N=164		P
	N or mean or media	% or SD or IQR	N or mean or media	% or SD or IQR	N or mean or media	% or SD or IQR	
Age, years	57.0	10.1	49.7	11.0	49.4	11.4	<0.0001
Male sex	48	75.0%	121	73.8%	121	73.8%	0.98
Caucasian	61	95.3%	144	87.8%	145	88.4%	0.23
BMI, kg/m^2	25.6	4.3	26.5	5.4	25.7	4.3	0.27
Risk factors for HIV acquisition							0.02
Sexual	44	68.8%	121	73.8%	92	56.1%	
IVDU	9	14.1%	20	12.2%	30	18.3%	
Other or unknown	11	17.2%	23	14.0%	42	25.6%	
HbsAg-positive (45 missing)	1	1.7%	14	9.4%	11	7.9%	0.17
HIV-Ab positive	14	21.9%	22	13.4%	38	23.2%	0.04
Detectable HIVRNA (>50 copies/mm^3)	6	9.4%	12	7.3%	26	15.9%	0.04
CD4, cells/mm^3	663	504-907	734	500-964	608	438-846	0.005
CD4/CD8 ratio	0.85	0.62-1.27	0.93	0.66-1.27	0.80	0.50-1.20	0.19
Previous treatment duration, years	21.5	9.9-25.4	9.7	4.5-16.1	8.7	3.4-17.1	<0.0001
Previous regimen included							
TDF	1	1.6%	40	24.4%	9	5.5%	<0.0001
PI	38	59.4%	20	12.2%	21	12.8%	<0.0001
INSTI	49	76.6%	68	41.5%	108	65.9%	<0.0001
NNRTI	13	20.3%	78	47.6%	18	11.0%	<0.0001
Hypertension	31	48.4%	39	23.8%	42	25.6%	0.0006
Diabetes	7	10.9%	4	2.4%	15	9.1%	0.02
Dyslipidemia	31	48.4%	46	28.0%	45	27.4%	0.005
On statin treatment	19	29.7%	25	15.2%	26	15.9%	0.03
On lipid-lowering treatments	20	31.3%	31	18.9%	30	18.3%	0.07
Total cholesterol, mg/dL	192	51	203	43	194	40	0.10
LDL-c, mg/dL	111	42	125	37	110	34	0.0006
HDL-c, mg/dL	48	16	49	15	54	20	0.01
Triglycerides, mg/dL	144	101-199	121	84-175	117	85-182	0.14

Figure 1. Change from baseline.









Masiello A.

The dangerous liaisons: Correlation between lipid profile, subclinical atherosclerosis, hepatic steatosis and hepatic fibrosis in PLWH

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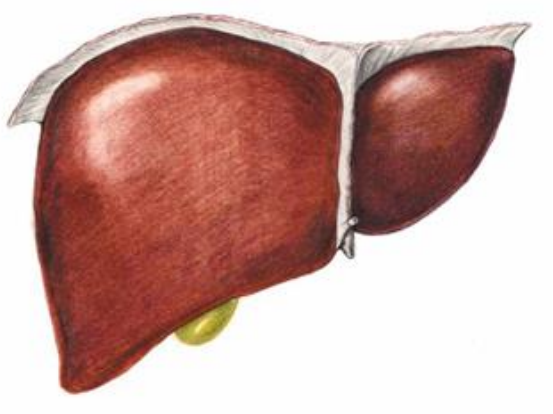
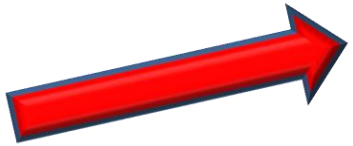
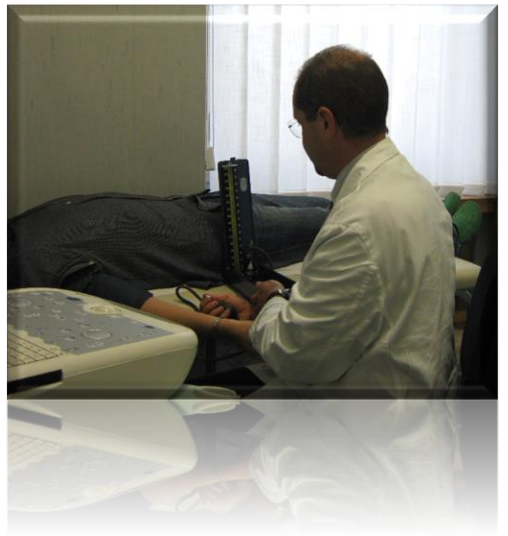


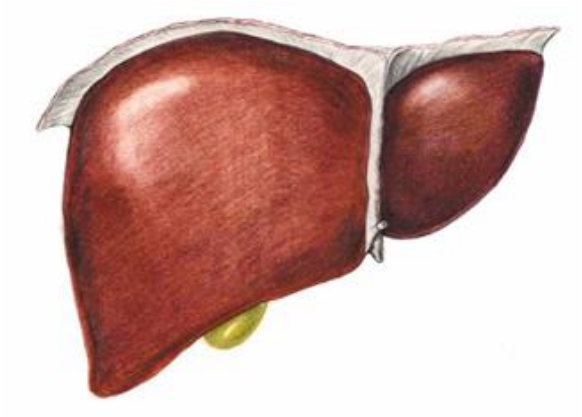


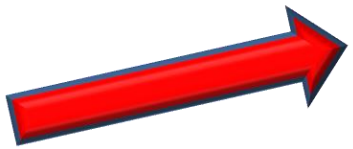


BASELINE DATA	TOTAL	IMT< 1,3	IMT≥ 1,3	p
Numbers of patients	128	85	43	///
Age, median (range)	52 (26-84)	49 (26-84)	59 (32-77)	///
Male patients n(%)	95 (74,2)	67 (78,8)	28 (65,1)	0,09
Years on HAART, median (range)	11 (1-35)	8,5 (1-26)	18 (7-35)	///
ARV Regimens n (%)	DUAL 31 (24,2) 2NRTI+PI 7 (5,4) 2NRTI+INSTI 67 (52,3) 2NRTI+1NNRTI 23 (17,9)	DUAL 24 (28,2) 2NRTI+PI 1 (1,1) 2NRTI+INSTI 40 (50,5) 2NRTI+ 1NNRTI 20 (18,8)	DUAL 7 (16,2) 2NRTI+PI 6 (13,9) 2NRTI+INSTI 27 (62,7) 2NRTI+1NNRTI 3 (6,9)	0,2 **0,009** 0,13 **0,03**
CD4, cell/uL, M +SD	672,22±313,41	657,96±292	700±352,7	047
CD4+ NADIR , cell/µL (M ± SD)	294,87±266,67	330,83±225,91	245,42±211	**0,04**
CD4/CD8 ratio>1 n (%)	58 (45,3)	46 (54,1)	12 (27,9)	**0,008**
Triglycerides (mg/dl) M± SD	118±66,95	110,86±60,29	140,73±77,61	**0,01**
Total cholesterol (mg/dl) M ± SD	190±40	184,4±39,2	201,2±39,7	**0,01**
HDL cholesterol (mg/dl) M ± SD	55,51±17,61	54,81±13,37	57,13±14,09	0,36
LDL cholesterol (mg/dl) M± SD	113,6±35,38	101,39±30,56	120,81±38,42	**0,002**
% of Elevated Triglycerides >150 mg/dl	50 (39)	15 (17,6)	35 (81,4)	**0,0000**
% of Elevated Cholesterol > 200 mg/dl	46 (35,9)	14 (16,4)	32 (74,4)	**0,0000**
Liver stiffness>F2, n (%)	24 (18,7)	12 (14,11)	12 (27,9)	0,09
Steatosis grade (CAP score>260 dB/m) n (%)	48 (37,5)	24 (28,5)	24 (55,8)	**0,004**

Iodice V.

Correlation between lipid profile, subclinical atherosclerosis, hepatic fibrosteatosis and bone mineral density in PLWH: comparison between TAF/FTC/BIC and TDF/3TC/DOR.





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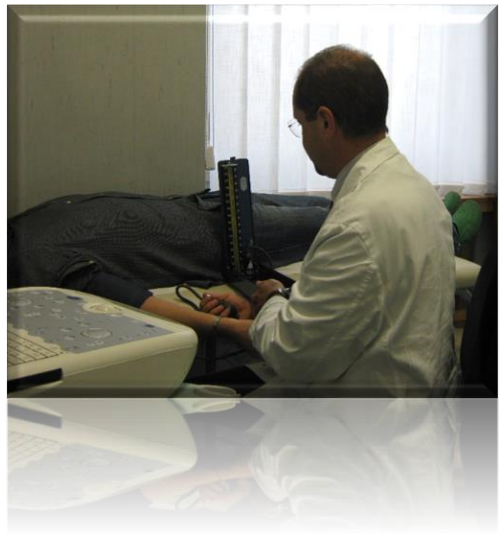

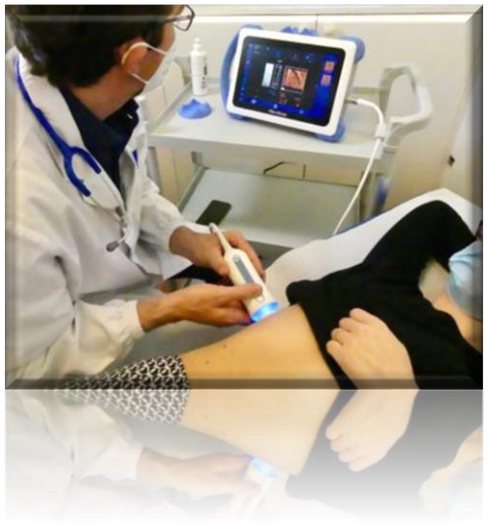

PATIENT DATA	TDF/3TC+DOR	TAF/FTC+BIC	p
Numbers of patients	20	20	///
Age, median (range)	45 (30-72)	45 (30-72)	///
Male patients n(%)	15 (75)	15 (75)	///
Years on HAART, median (range)	12 (8-24)	18 (12-24)	///
CD4, cell/uL M + SD	592 ± 268,6	607,16 ± 263,19	0,192
CD4+ NADIR , cell/µL (M ± SD)	291,37± 124,81	313,94 ± 180,64	4.329
CD4/CD8 ratio>1 n (%)	8 (40)	10 (50)	0
WBC (10^3/µL) M ± SD	7192,6 ± 2192,7	6218,8 ± 1628,33	16,903
RBC (10^6/µL) M ± SD	4654,74 ± 440,4	4952,77 ± 577,28	9,87
HB g/dl M ± SD	15,7± 1,5	14,61 ± 0,93	0,088
PLT (10^3/µL) M ± SD	192,9 ± 77,64	196,94 ± 57,40	2,578
Fibrinogeno (mg/dl) M ± SD	295,47 ± 70,46	280,05 ± 63,45	0,471
PCR (mg/dl) M ± SD	0,19 ± 0,18	0,11 ± 0,15	0,005
Triglycerides (mg/dl) M± SD	130,1± 64,65	147,23 ± 126,91	0,593
Total cholesterol (mg/dl) M ± SD	170,16 ± 31,93	201,16 ± 32	0,004
HDL cholesterol (mg/dl) M ± SD	45,27 ±16,02	48,64 ± 10,45	0,435
LDL cholesterol (mg/dl) M± SD	94,67 ± 29,56	110,17 ± 28,84	0,101
% of Elevated Triglycerides >150 mg/dl	7 (35)	3 (15)	0,00997
% of Elevated Cholesterol > 200 mg/dl	4 (20)	3 (15)	0,01997
>0,9 IMT <1.3	3 (15)	8 (40)	0,00204
IMT > 1,3	0	1 (5)	//

AST (U/L) M ± SD	25,26 ± 11,35	19,72 ± 7,87	0,0808
ALT (U/L) M ± SD	23,42 ± 11,60	19,33 ± 9,02	0,220
GGT (U/L) M ± SD	27,53 ± 17,35	19,94 ± 8,78	0,089
ALP (U/L) M ± SD	77,58 ± 23,89	62,70 ± 19,27	0,0365
Bilirubin total (mg/dl) M ± SD	0,7 ± 0,53	0,64 ± 0,49	0,712
Bilirubin direct (mg/dl) M ± SD	0,26 ± 0,205	0,26 ± 0,13	1
Liver stiffness >F2, n (%)	4 (20)	1 (5)	0.18695
Steatosis grade (CAP score>260 dB/m) n (%)	4 (20)	6 (30)	0.00194
Vitamin D (ng/ml)	25,46 ± 12,58	19,90 ± 15,96	0,228
% of patients with T/Z score alterations n (%)	5 (25)	6 (30)	0.00092
Azotemia (mg/dl) M+SD	14,36 ± 4,22	23,53 ± 23,27	0,091
Creatininemia (mg/dl) M+SD	0,93 ± 0,21	0,97 ± 0,15	0,492
Uricemia (mg/dl) M+SD	6,47 ± 3,78	5,08 ± 1,82	0,146
eGFR (≥ 80 ml/min) n (%)	16 (80)	15 (75)	0

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*