18ª edición

POSTCROI 2021

Una actualización de la 28ª Conference on Retroviruses and Opportunistic Infections

Envejecimiento e inflamación

Eugènia Negredo

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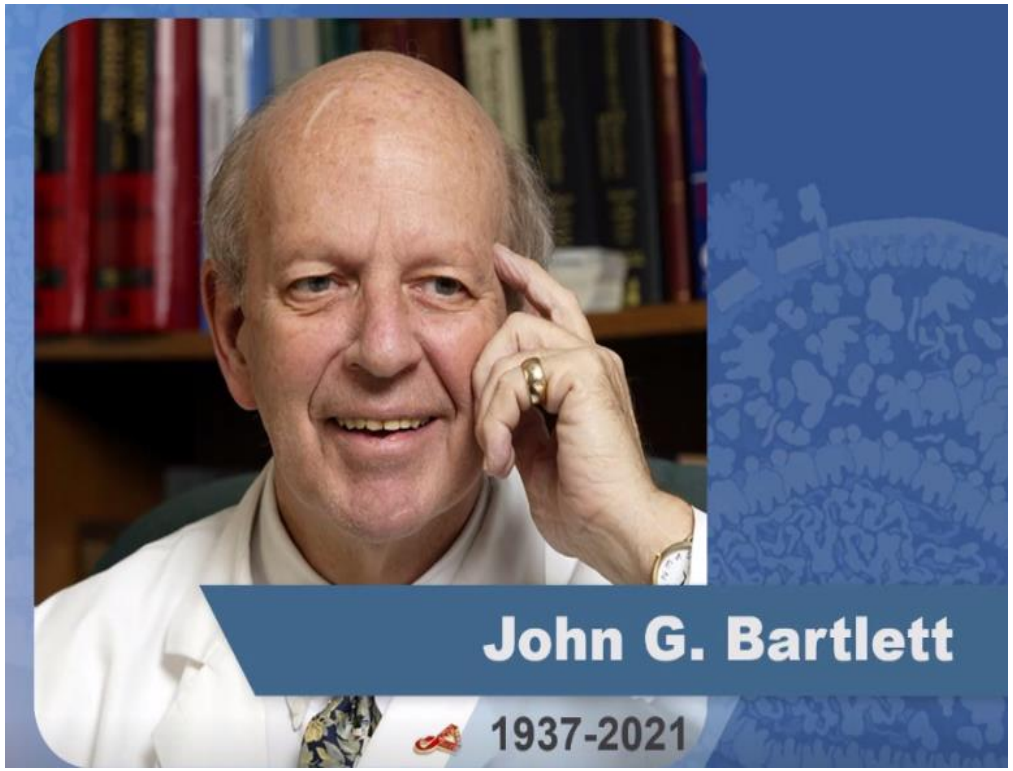
IN MEMORIAM



ÓSEO y RENAL

SHORT-COURSE ALENDRONATE FOR THE PREVENTION OF ART-ASSOCIATED BONE LOSS

Study Endpoints

Primary endpoint:

- Between-group difference in percentage change in TH-BMD from baseline to week 50 among participants who received at least one dose of study medication

Secondary endpoints:

- Between-group differences in percentage change in LS BMD to week 50
- Between-group differences in percentage change in TH and LS BMD at weeks 14 and 26
- To assess the safety and tolerability of oral Alendronate in PWH initiating ART

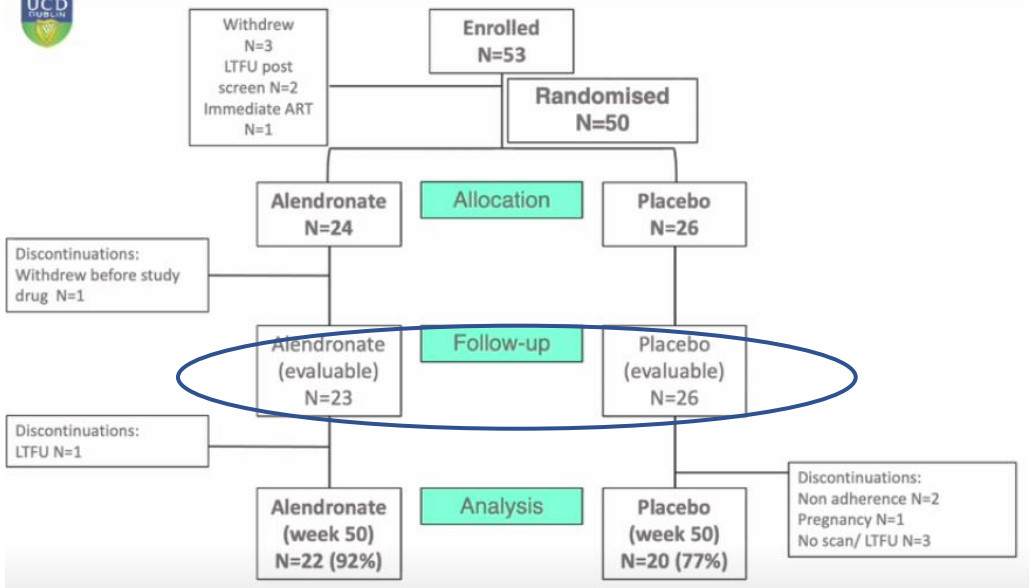
Inclusion Criteria

- male>25 years old or female>30 years old
- HIV-1 antibody positive (no CD4 or HIV RNA criteria)
- antiretroviral therapy naïve
- eligible for initiation of antiretroviral therapy

Exclusion Criteria

- history of osteoporosis or fracture
- chronic renal failure
- hypocalcaemia/ hypercalcaemia
- previous treatment/allergy to bisphosphonates
- recent history of any abnormality of the oesophagus
- recent invasive dental work
- recent significant steroid exposure
- pregnancy or breastfeeding

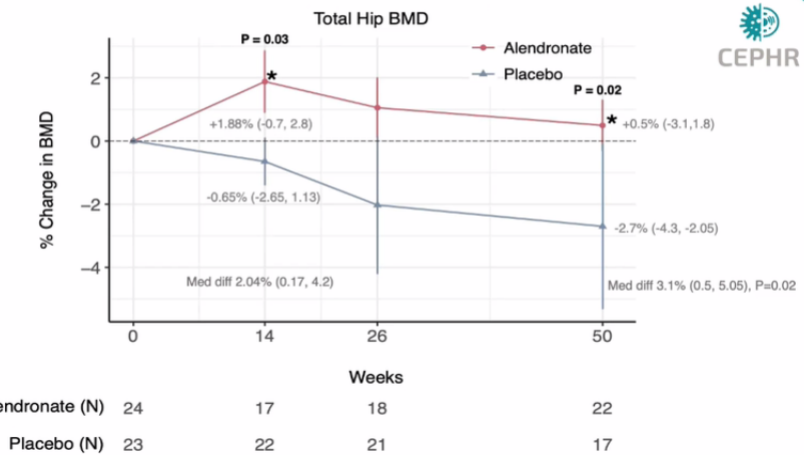
Enrollment and follow-up



Baseline Characteristics

	Overall (N = 50)	Alendronate (N = 24)	Placebo (N = 26)
Age (years)	35 (32, 40)	36 (32, 39)	34 (31, 41)
Male n (%)	43 (86.0%)	20 (83.3%)	23 (88.5%)
Ethnicity n (%)			
African origin	17 (34.0%)	10 (41.7%)	7 (26.9%)
Caucasian	23 (46.0%)	7 (29.2%)	16 (61.5%)
South American	10 (20.0%)	7 (29.2%)	3 (11.5%)
Smoking status n (%)			
Current smoker	18 (36.0%)	7 (29.2%)	11 (42.3%)
Ex-smoker	8 (16.0%)	2 (8.3%)	6 (23.1%)
Never smoked	22 (44.0%)	14 (58.3%)	8 (30.8%)
Unknown	2 (4.0%)	1 (4.2%)	1 (3.8%)
BMI (kg/m2)	24.0 (22.3, 26.9)	24.5 (22.9, 29.0)	23.2 (22.1, 25.7)
Prior falls: Yes (n (%)	2 (4.0%)	0 (0.0%)	2 (7.7%)
*History of fractures: Yes n (%)	10 (20.0%)	8 (33.3%)	2 (7.7%)

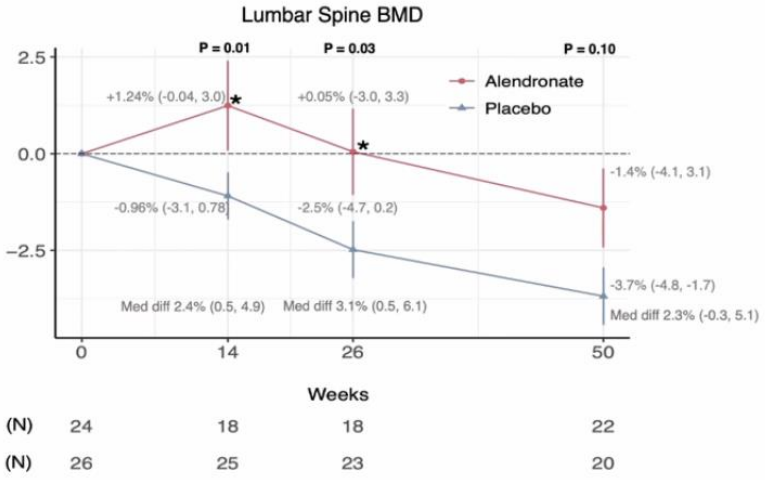
Percentage change in BMD at Total Hip



Treatment Emergent Adverse Events

	Alendronate (N=23) n (%[a])	Placebo (N=26) n (%[a])	P
Treatment Emergent Adverse Events			
Any Treatment Emergent Adverse Events	18 (78.2)	18 (69.2)	0.53
[¥]Any Treatment-Related Emergent AE	12 (52.2)	10 (38.5)	0.40
Resulting in study drug discontinuation	0 (0.0)	3 (11.5)	0.24
Any Serious Adverse Event	2 (8.7)	5 (19.2)	0.42
Treatment emergent Adverse events by grade			
Mild	16 (69.7)	15 (57.9)	
Moderate	2 (8.7)	3 (11.5)	
Severe	0 (0.0)	0 (0.0)	

Percentage change in BMD at Lumbar Spine



Conclusions

- Short course (14 weeks) generic oral Alendronate at ART initiation prevented ART-associated bone loss over 48 weeks at TH
- A protective effect was also observed at the LS but was limited to the first 24 weeks
- Even in PWH on contemporary ART regimes, BMD loss at ART initiation is still evident
- Generic Alendronate is an inexpensive, easily accessible, safe and well tolerated option for preventing bone loss associated with ART initiation – this may be particularly important in resource limited settings
- Further analysis of bone turnover markers and immunological markers may give further mechanistic insights

SAFETY OF TENOFOVIR ALAFENAMIDE (TAF) IN PATIENTS WITH A HISTORY OF PROXIMAL RENAL TUBULOPATHY ON TDF

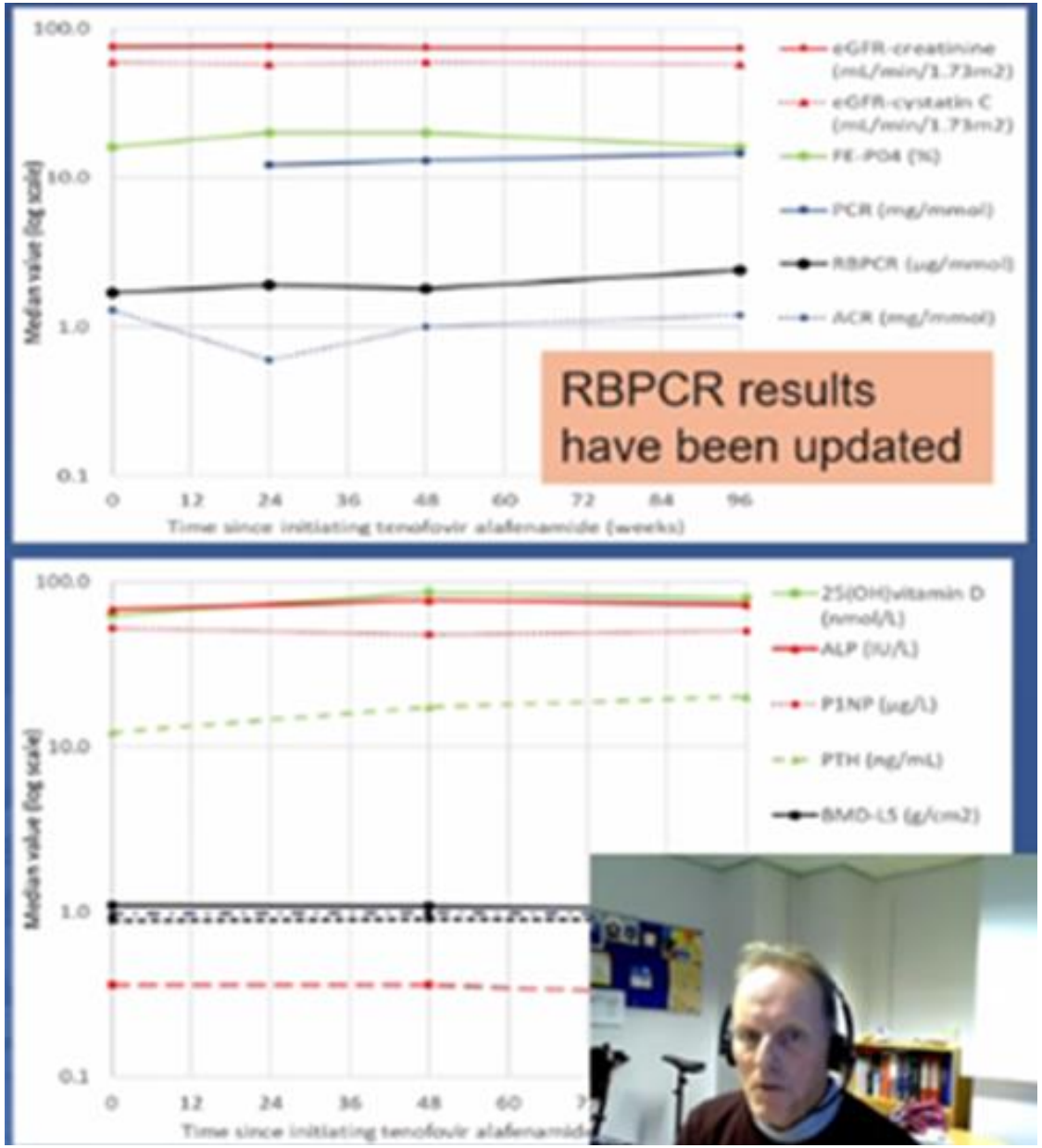
Frank A. Post

- Study objective: To assess the safety of TAF in people with HIV who developed treatment-limiting PRT while receiving TDF.
- Hypothesis: TAF exposure in this group of individuals would not resu PRT and have minimal impact on renal and bone biomarkers.

Methods

- We conducted a multicentre, open-label, single arm switch study (EudraCT: 2016-003345-29)
- We enrolled participants with HIV who experienced treatment-limiting PRT while receiving TDF
  - Histology (acute tubular injury), or ≥2 of
  - Proteinuria, normoglycaemic glycosuria, hypophosphatemia, rapid eGFR decline
- Participants initiated TAF and were followed up every 12 weeks for 96 weeks; modifications to the ART regimen were allowed
- We analyzed renal and bone biomarkers using multi-level mixe linear regression models

- 31 participants (median age 55 years, 97% male, 87% white)
- All remained on TAF at week 96
- None developed recurrent PRT or Fanconi syndrome



- During 96 weeks of follow up, none of the participants developed recurrent PRT, glycosuria, sustained hypophosphataemia or worsening total proteinuria.
- Additional biomarker analyses showed eGFR-cystatin C, albuminuria, RBPCR, fractional excretion of phosphate, markers of bone turnover and BMD remained stable from baseline.
- These results suggest that TAF is a treatment option for people with HIV who experienced PRT or Fanconi syndrome while taking TDF
- Follow up continues for a further three years to provide additional data for TAF in this population.

NEUROCOGNITIVO

12-Year Cognitive Decline is Associated with Lung Disease, Diabetes, and Depression

Scott Letendre, M.D.

Background

- Cognitive impairment is more common in people with HIV (PWH) than in the general population and is associated with worse quality of life and worse health outcomes.
- Most studies of cognitive change in PWH have focused on decline over a few years but no projects have assessed cognitive change and its correlates over more than a decade in all participants.
- To address this key gap, the 6-site, U.S. CHARTER project reassessed 397 participants 12 years after their initial assessment.

Methods

- Standardized, comprehensive neuromedical and neuro-cognitive assessments were performed at the initial and 12-year timepoints and included:
  - Neuropsychological test battery that assessed 7 cognitive domains
  - Medical history & exam, prescribed medications, drug use, and venipuncture.
- The cognitive outcome was regression-based change score (RBCS), which was calculated using normative data from people with and without HIV.
  - Decline was defined as change worse than the 5th percentile of the normative data.
- Demographic, disease, drug use, and therapy characteristics were analyzed using multivariable regression with α=0.15 for covariate inclusion.

CHARTER

Participant Characteristics (N=39

	Visit 1	Visit 2		Visit 1	Visit 2
Age (years)[1]	43.6	56.3	Global Deficit Score[3]	0.39	0.38
Duration of HIV (years)[1]	9.9	22.6	RBCS[2]	-	-0.28
Duration of ART (years)[1]	4.9	15.3	Global Cognitive Decline[2,*]	-	23.4%
Sex (Women)[2]	24.4%	-	Beck Depression Inventory[3]	11	7
Race (Black)[2]	46.6%	-	Current Major Depressive Disorder[2]	12.8%	7.0%
Ethnicity (Hispanic)[2]	10.8%	-	Diabetes[2]	6.5%	20.2%
Education (years)[1]	13.2	13.3	Chronic Lung Disease[2]	9.3%	19.9%
Body Mass Index[3]	25.8	26.2	Hypertension[2]	18.9%	48.6%
Nadir CD4+ Count (/μL)[3]	172	114	Hyperlipidemia[2]	9.8%	38.0%
AIDS Diagnosis[2]	61.4%	72.8%	HCV Seropositive[2]	23.9%	35.0%
On ART[2]	74.8%	96.7%	Lifetime Alcohol Use Disorder	53.1%	57.9%
CD4+ T-Cell Count (/μL)[3]	453	591	Lifetime Cocaine Use Disorder	40.3%	42.3%
Plasma HIV RNA ≤ 200*	71.0%	91.9%	Lifetime Cannabis Use Disorder	27.4%	31.7%
CSF HIV RNA ≤ 50*	87.3%	94.2%	Lifetime Opioid Use Disorder	14.6%	16.4%

[1]Mean, [2]Percent, [3]Median *Among those on ART n for CSF: 229 at V1, 191 at V2

Associations with Global Cognitive Change

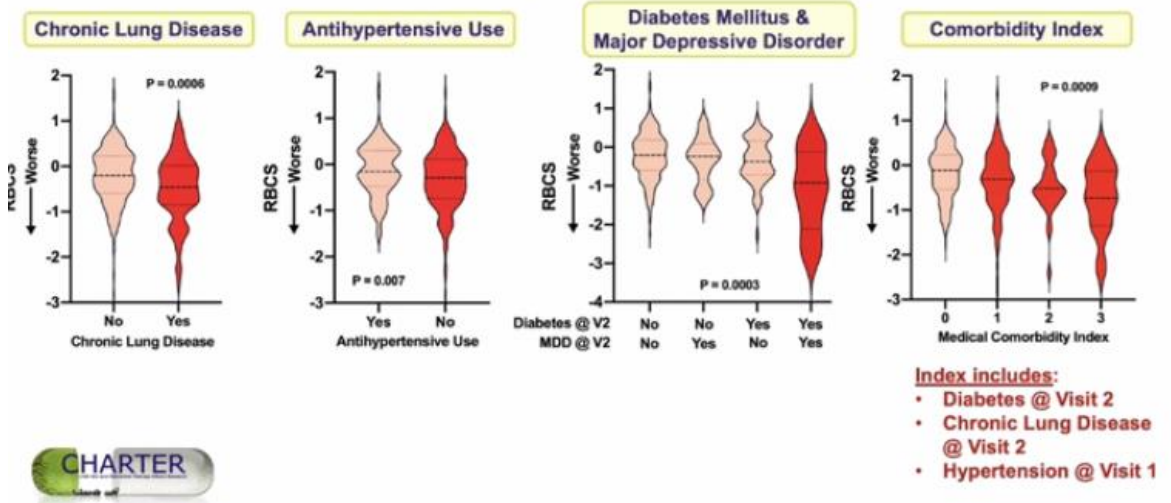
	Visit	β	P value	β	P value	FDR P value	Risk Direction
Diabetes Mellitus	2	0.099	0.0159	0.219	0.0008	0.004	Present
Chronic Lung Disease	2	0.139	0.0006	0.103	0.010	0.021	Present
Current Major Depressive Disorder	2	0.159	0.0097	0.180	0.006	0.016	Present
Lifetime Cannabis Use Disorder	1	0.075	0.036	0.081	0.029	0.043	Present
Duration of ART	1	-0.001	0.066	-0.001	0.043	0.048	Longer
Hypertension	1	0.072	0.081	0.119	0.011	0.021	Present
Age	1	0.003	0.509	0.008	0.062	0.062	Younger
Sex	1	-0.047	0.535	-	-	-	-
Race/Ethnicity	1	-0.001	0.797	-	-	-	-
Current MDD x Diabetes	-	-	-	-0.136	0.039	0.048	See Graph
Antihypertensive Use	2	0.200	0.007	0.308	0.0003	0.001	Non-Use

CHARTER

FDR = False Discovery Rate

Model $R^2 = 0.139$, $P < 0.0001$

Graphs of Associations with Global Cognitive Change



Index includes:
- Diabetes @ Visit 2
- Chronic Lung Disease @ Visit 2
- Hypertension @ Visit 1

CHARTER

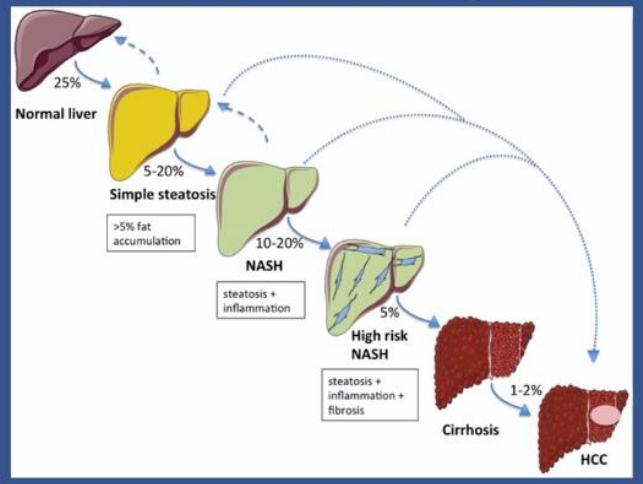
- Over a median of 12.4 years of follow-up, nearly a quarter of PWH who were on suppressive ART experienced cognitive decline
  - Compared with an estimated 5% of people without HIV
- The magnitude of decline was not severe in most participants and was associated with previously reported aging-related risk factors (e.g., diabetes) as well as with less frequently reported risk factors, such as
  - Chronic Lung Disease
  - Major Depressive Disorder
  - Lifetime Cannabis Use Disorder
- When the CHARTER cohort was first assembled between 2003 and 2007, it was designed to reflect – and generalize to – PWH who receive outpatient healthcare in the U.S. but these 12-year findings may be affected by survivor bias and other biases

ESTEATOSIS HEPÁTICA

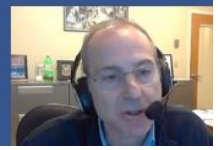
MECHANISMS AND TREATMENTS FOR STEATOSIS IN HIV

Steven Grinspoon, M.D.

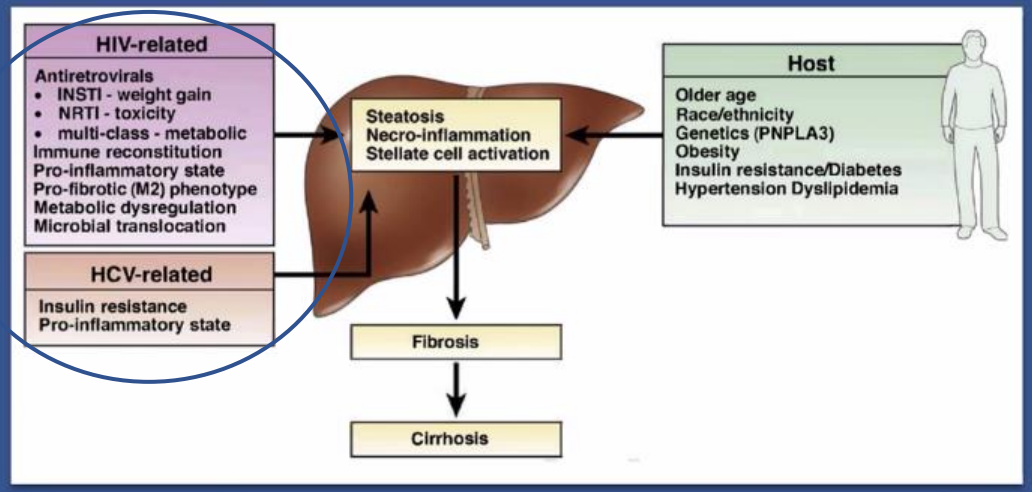
NAFLD: A Spectrum of Progressive Disease



Segheiri, *Frontiers in Endocrinology 2018*

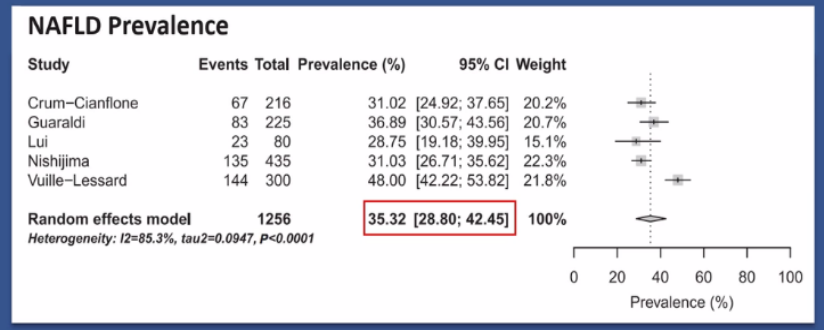


Pathogenesis of NAFLD in HIV



Lake et al, *Clin Gastroenterol and Hepatol* 2020

Prevalence of NAFLD in HIV

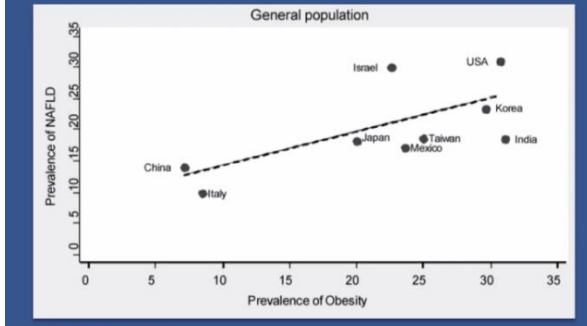


Risk Factors for NAFLD in HIV

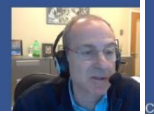
- BMI
- Waist circumference
- Type 2 diabetes
- High CD4 count

Maurice et al, *AIDS* 2017

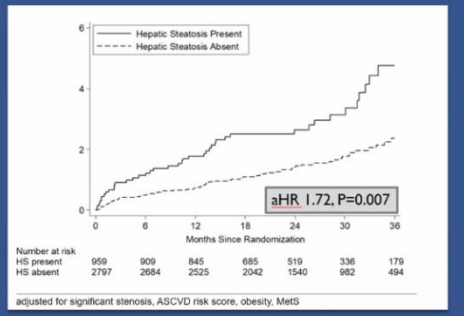
NAFLD as a Manifestation of Metabolic Disease



Lazo, *Semin Liver Dis* 2008

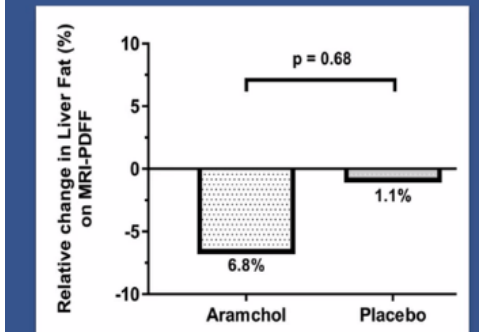


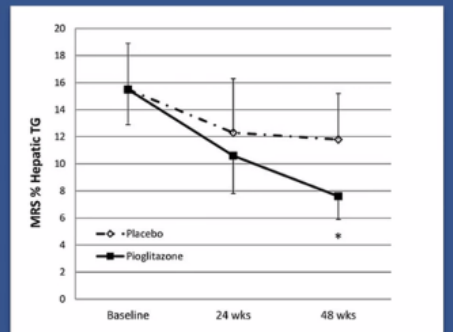
NAFLD Patients at Increased Risk of CVD



Corey, In Press 2020

Agents Investigated for Effects on Steatosis in HIV

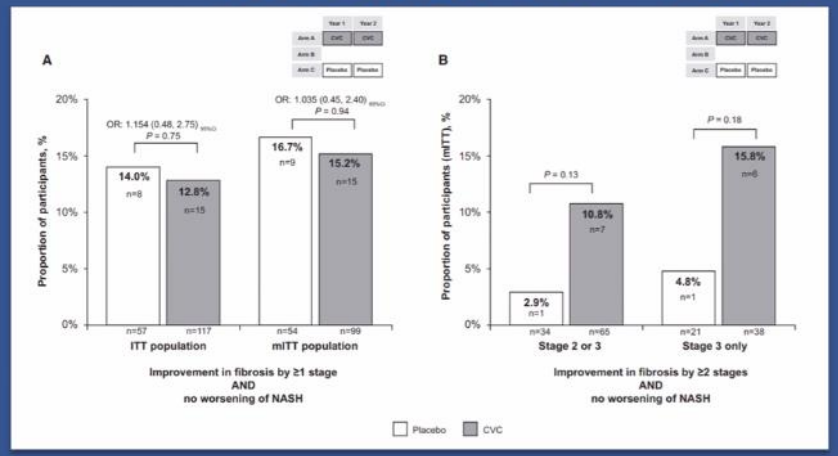




Aramchol
Steroyl CO-A Desaturase Inhibitor
Decreases Fatty Acid Synthesis
N=50 RCT
No effect on hepatic steatosis
Unlikely to move forward
Ajmera Hepatology 2019

Pioglitazone
PPAR-gamma agonist
Affects critical adipogenic pathways
N=13 RCT
Within group effect only
Approved for DM, edema, bladder ca
Mathews AIDS Hum Retro 2015

Effects of Cenicriviroc in NAFLD/NASH The Centaur Trial - Non HIV

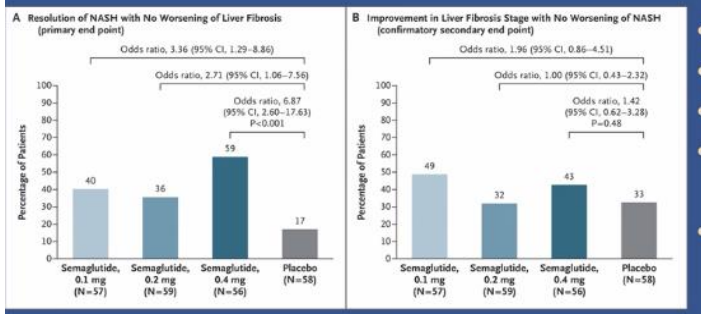


Ratziu, *Hepatology* 2020

GLP-1 Agonists

- Increase insulin secretion, decrease appetite, delay gastric emptying, reduce weight
- Multiple salient properties with respect to lipid metabolism and insulin sensitivity in the liver

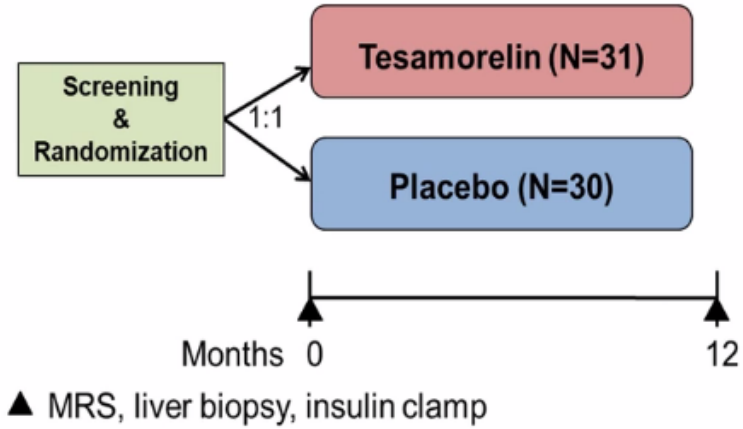
Semaglutide, GLP1 Agonist, for NAFLD



- Approved for DM
- Confirmed NAFLD by Bx
- 65% DM, BMI 36
- Effects on steatosis not reported
- 15% weight loss in highest dose

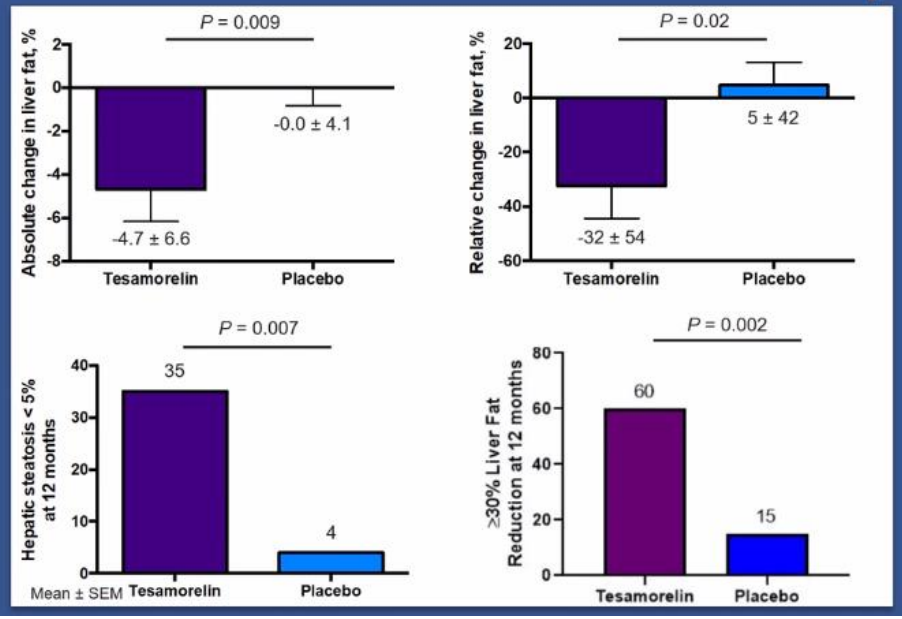
Newsome, *NEJM* 2020

- HIV on stable ART
- Hepatic fat ≥ 5% on MRS, without significant ETOH, viral hepatitis
- Primary Endpoint, Hepatic Fat

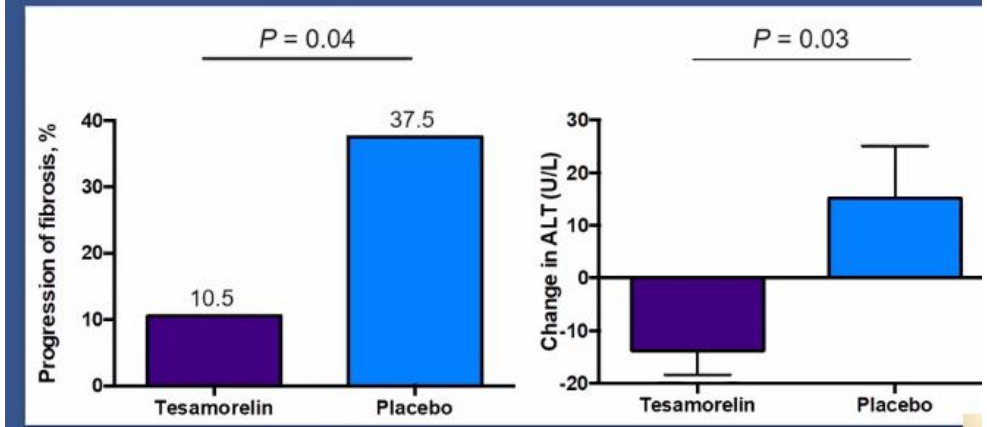


Stanley, Fourman, *The Lancet HIV* 2019

Effect of Tesamorelin on Hepatic Fat



Effect of Tesamorelin on Fibrosis Progression and ALT*



*ALT > 30 U/L at Baseline

- Change in CRP also significant
- No change in glucose

Lifestyle

- First line therapy
- Weight loss
  - > 7%, associated with improved steatosis NAS score, no change fibrosis
  - 7-9%, 64% with NASH resolution
  - >10%, 45% with fibrosis regression > 1 stage
- Studies in HIV lacking

Younossi, *AGA Clinical Guidelines* 2020

INFLAMACIÓN

Effects of Switch from 3DR to 2DR on Inflammatory Biomarkers

Sergio Serrano-Villar
Hospital Universitario Ramón y Cajal
Madrid, Spain

Objective: To assess the effects of switching ART from triple therapy (TT) to 2DR on long-term trajectories of inflammatory markers.

Methods

Design: Nested study in the Spanish AIDS Cohort (CoRIS)

Inclusion criteria

- Patients initiating ART in CORIS between 2004-2018 with TT (2NRTI+bPI/INSTI).
- Virological suppression achieved in the first 48 weeks of ART.
- Either remained on TT or switched to 2DR (3TC+bPI, 3TC+DTG, RPV+DTG) or 1DR (LPVr or bDRV).
- At least 3 plasma samples available

Exclusion criteria

- ART initiation with regimens with <3 drugs
- Virological failure: ≥2 consecutive viral loads more than 50 copies/mL) during the first 48 weeks of ART
- AIDS conditions or serious non-AIDS events (malignancies, cardiovascular disease, end-stage liver disease, end-stage kidney disease), in the first 48 weeks of ART.

From 14,458 patients, 8,416 met these criteria

90 patients on 3DC
60 patients on 2DC
30 patients on 1DC

Selected based on
At least 3 samples
Longer follow-up

IL-6, hsCRP
sCD14, sCD163
D-dimers
IFABP

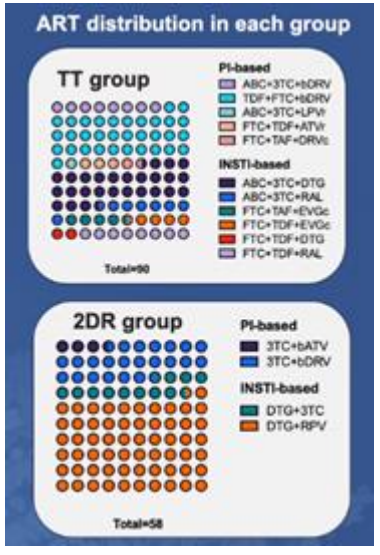
Statistics

- Plasma samples measured in duplicate using comercial ELISA kits.
- Linear trajectories estimated using piecewise linear mixed models with fixed effects (interaction term biomarker concentration#time, age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

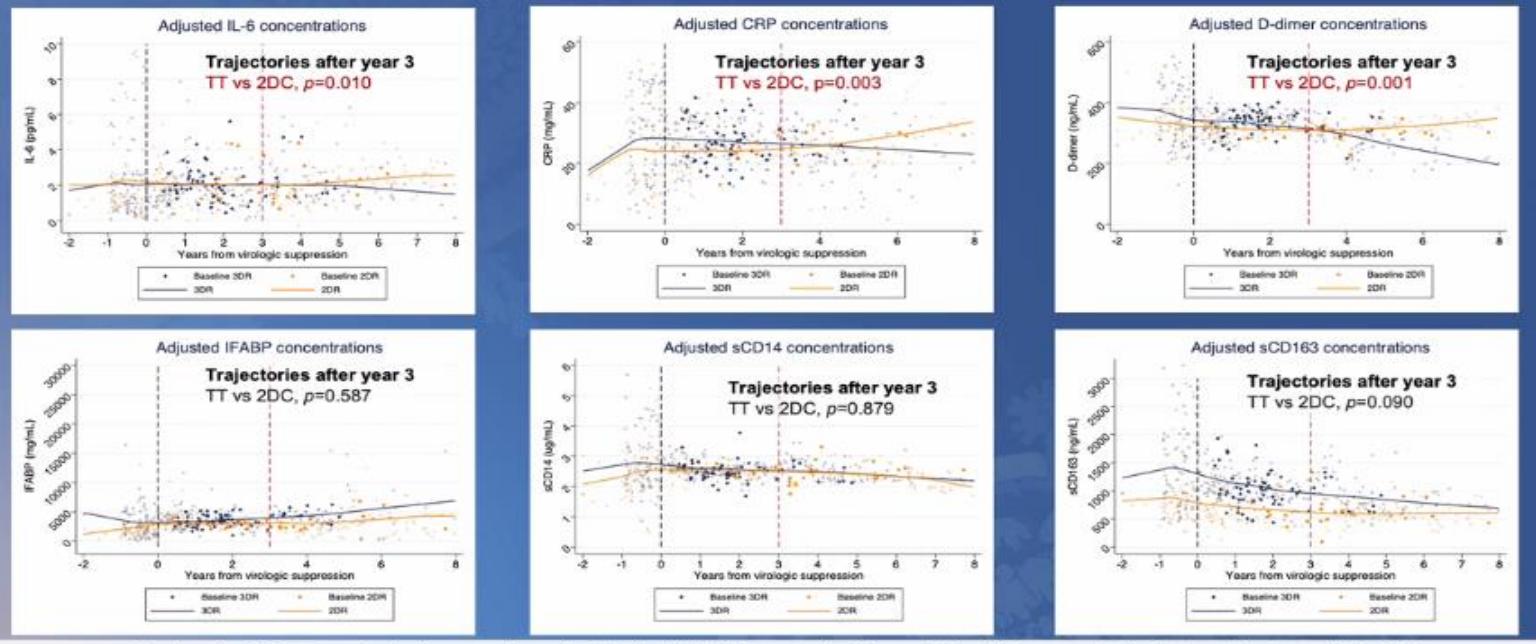
Results

General characteristics

	TT N=90	2DR N=58	p value
Age (mean, [SD])	37 (9)	40 (11)	0.227
Male, n (%)	78 (87)	50 (86)	0.936
IDU, n (%)	6 (7)	3 (6)	0.972
Spanish origin, n (%)	59 (66)	36 (62)	0.666
University education, n (%)	22 (24)	18 (31)	0.593
AIDS diagnosis, n (%)	15 (16)	8 (14)	0.769
HCV positive ever, n (%)	12 (13)	6 (10)	0.570
Maximum HIV-1 RNA (c/mL), median (IQR)	114500 (33770-344426)	93599 (36307-219000)	0.376
Time from ART initiation to virologic suppression (years), median (IQR)	0.5 (0.2-0.9)	0.5 (0.3-0.9)	0.524
Time from virologic suppression (years) to ART switch, median (IQR)	-	3.5 (1.9-5.2)	-
Nadir CD4 cell count (cells/µL), median (IQR)	300 (151-373)	259 (112-382)	0.309
Number of samples analyzed, median (min, max)	4 (3-11)	3 (3-8)	<0.001
Follow-up (years), median (IQR)	3.9 (2.5-4.7)	5.3 (3.9-6.8)	<0.001



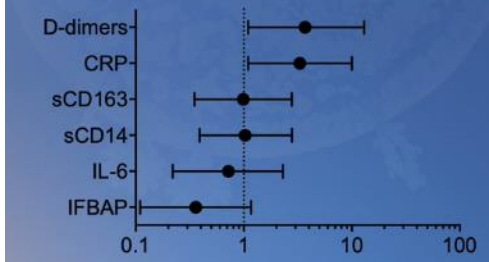
Adjusted Piecewise Linear Mixed Models



Baseline: for 3DR represents the the second sample after the HIV RNA suppression time point; for 2DR represents the first sample after switch to 2DR.
Linear trajectories estimated using **piecewise linear mixed models** with fixed effects (interaction term biomarker concentration#time, adjusted for age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

Results

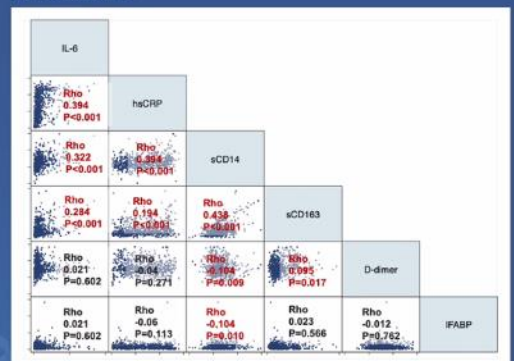
Multivariate Logistic regression: changes during follow-up TT (ref.) vs. 2DR



Adjusted Odds ratio for Quartile increase

Adjusted for age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression, years of follow-up

Crossed-correlations between inflammatory biomarkers

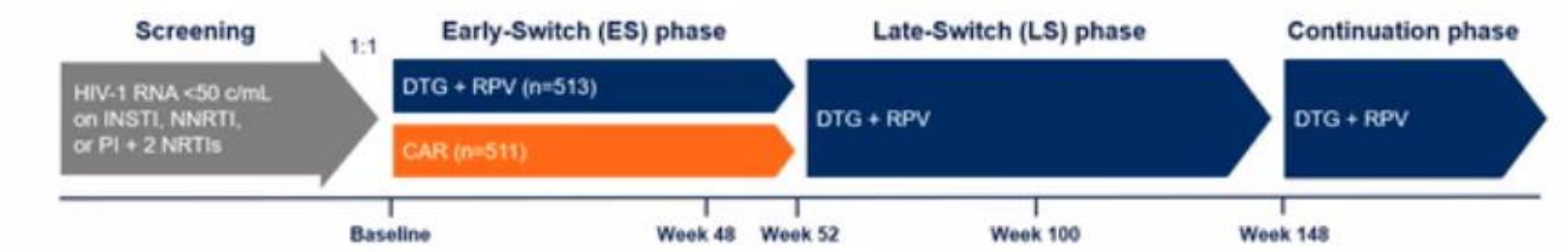


CONCLUSIONS

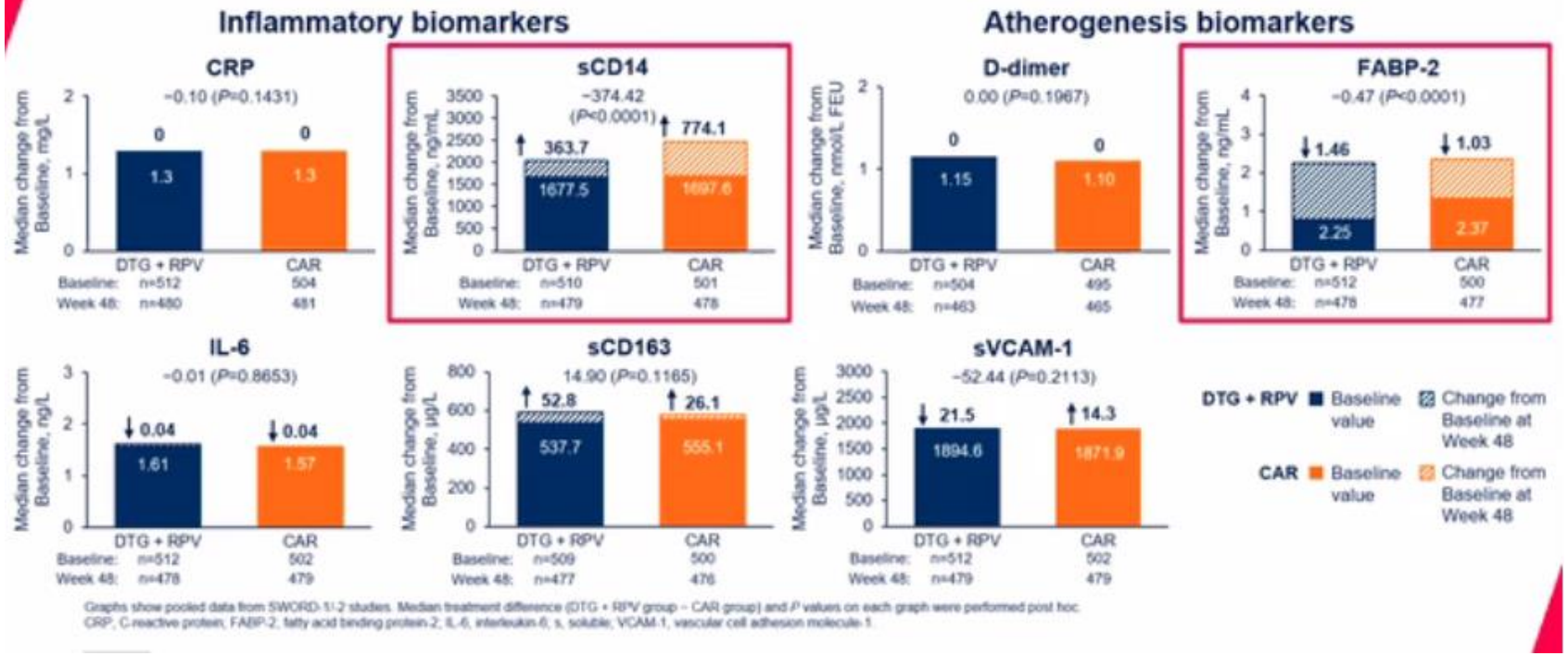
- In this observational study in virally suppressed individuals, maintaining 3DR was associated with a more favourable long-term anti-inflammatory profile than switching to 2DR.
- The potential clinical implications of these findings on the development of non-AIDS events deserve further investigation.

INFLAMMATORY AND ATHEROGENESIS MARKERS 148 WEEKS POST-SWITCH TO DTG + RPV IN SWORD-1/-2

Josep M. Llibre,[1] Luis Fernando López Cortés,[2] Alicia Aylott,[3] Brian Wynne,[4] Jessica Matthews,[4] Jean van Wyk,[5] Lesley P. Kahl[5]

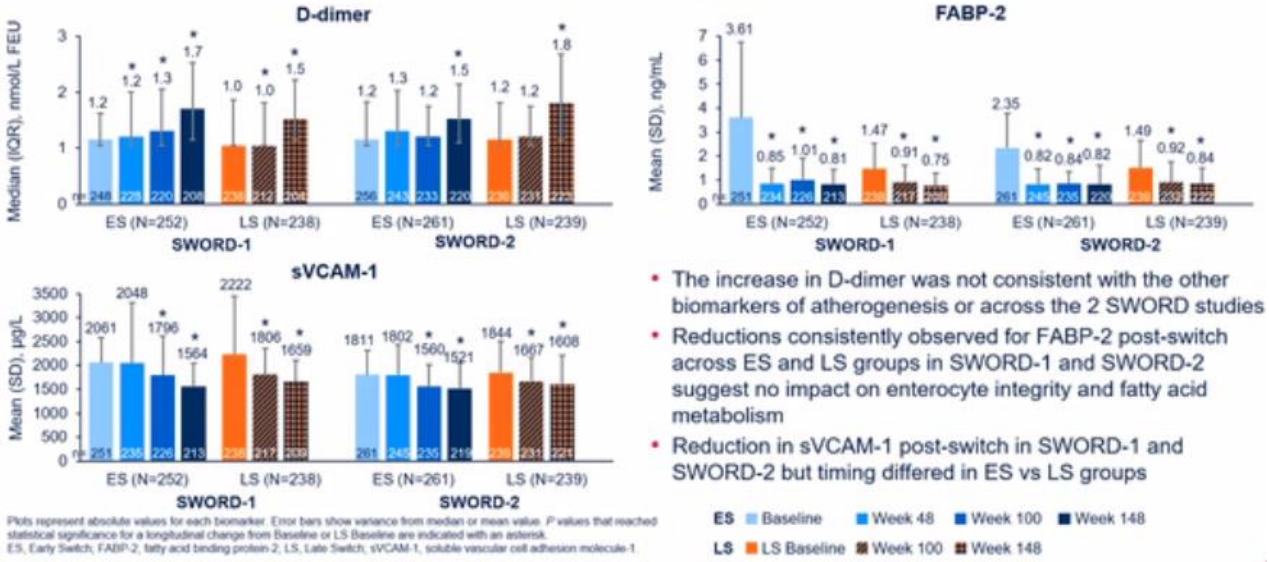


Controlled Early-Switch (ES) Phase: Change From Baseline to Week 48 Across Biomarkers



Graphs show pooled data from SWORD-1/-2 studies. Median treatment difference (DTG + RPV group − CAR group) and *P* values on each graph were performed post hoc.
CRP, C-reactive protein; FABP-2, fatty acid binding protein-2; IL-6, interleukin-6; s, soluble; VCAM-1, vascular cell adhesion molecule-1.

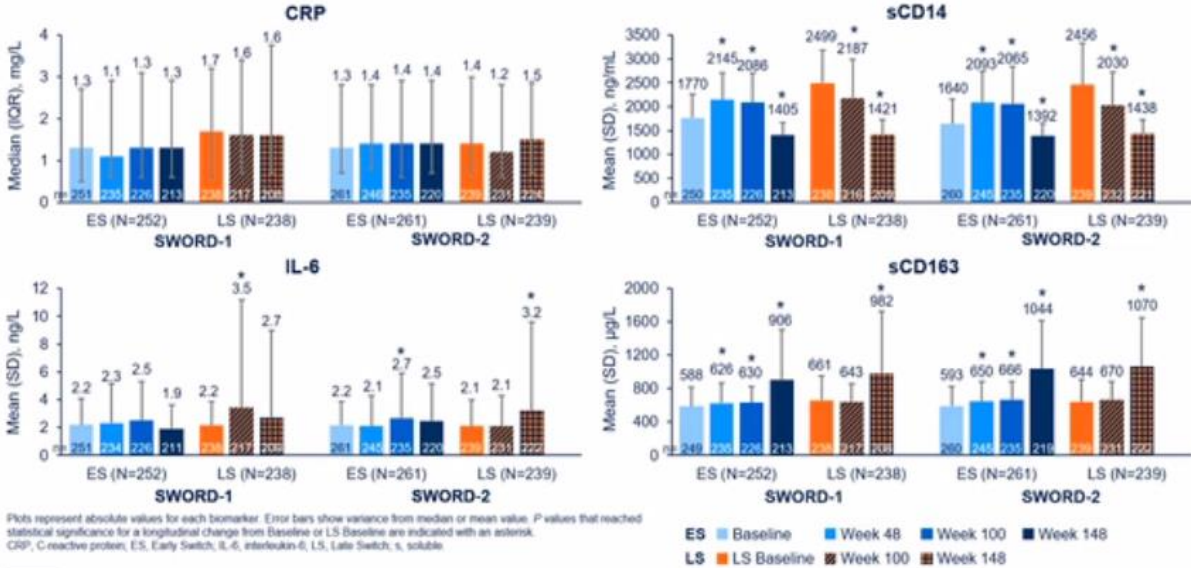
No Consistent Pattern of Change in Atherogenesis Biomarkers Was Observed Post-Switch to DTG + RPV Up to Week 148



- The increase in D-dimer was not consistent with the other biomarkers of atherogenesis or across the 2 SWORD studies
- Reductions consistently observed for FABP-2 post-switch across ES and LS groups in SWORD-1 and SWORD-2 suggest no impact on enterocyte integrity and fatty acid metabolism
- Reduction in sVCAM-1 post-switch in SWORD-1 and SWORD-2 but timing differed in ES vs LS groups

Plots represent absolute values for each biomarker. Error bars show variance from median or mean value. *P* values that reached statistical significance for a longitudinal change from Baseline or LS Baseline are indicated with an asterisk.
ES, Early Switch; FABP-2, fatty acid binding protein 2; LS, Late Switch; sVCAM-1, soluble vascular cell adhesion molecule-1.

No Consistent Pattern of Change Across Inflammatory Biomarkers Was Observed Post-Switch to DTG + RPV Up to Week 148



Plots represent absolute values for each biomarker. Error bars show variance from median or mean value. *P* values that reached statistical significance for a longitudinal change from Baseline or LS Baseline are indicated with an asterisk.
CRP, C-reactive protein; ES, Early Switch; IL-6, interleukin-6; LS, Late Switch; s, soluble.

Conclusions

- In the randomized controlled ES phase, comparison of change from Baseline to Week 48 in the DTG + RPV group vs the CAR group revealed no consistent patterns for inflammatory or atherogenesis biomarkers
- Longitudinally up to Week 148, no consistent pattern of change was observed after switch to DTG + RPV from CAR in
  - Inflammatory biomarkers: no change was observed in CRP, and the pattern of change was generally inconsistent across sCD14, IL-6, and sCD163
  - Atherogenesis biomarkers: FABP-2 and sVCAM-1 showed sustained reductions post-switch, and increases in D-dimer were inconsistent across both the ES and LS groups and across the 2 SWORD studies
- Overall, these results from SWORD-1 and SWORD-2 illustrate the lack of a consistent pattern of change in biomarkers post-switch to the 2DR DTG + RPV and hence provide no evidence for an association of increased inflammation or atherogenesis with the 2DR while maintaining virologic suppression

SEX MODIFIES THE ASSOCIATION BETWEEN INFLAMMATION AND VASCULAR EVENTS IN TREATED HIV

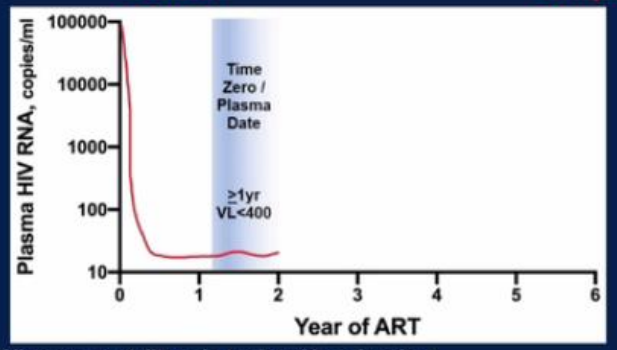
Study Design

CNICS CFAR Network Of Integrated Clinical Systems

Eligible Participants
N = 9,430

Random Selection → **Sub-Cohort N = 979** — 'Control'

All Events* → **Type 1 MI N = 76** — 'Comparator'; **Type 2 MI N = 56** — 'Comparator'; **Ischemic Stroke N = 30** — 'Comparator'; **VTE N = 80** — 'Comparator'

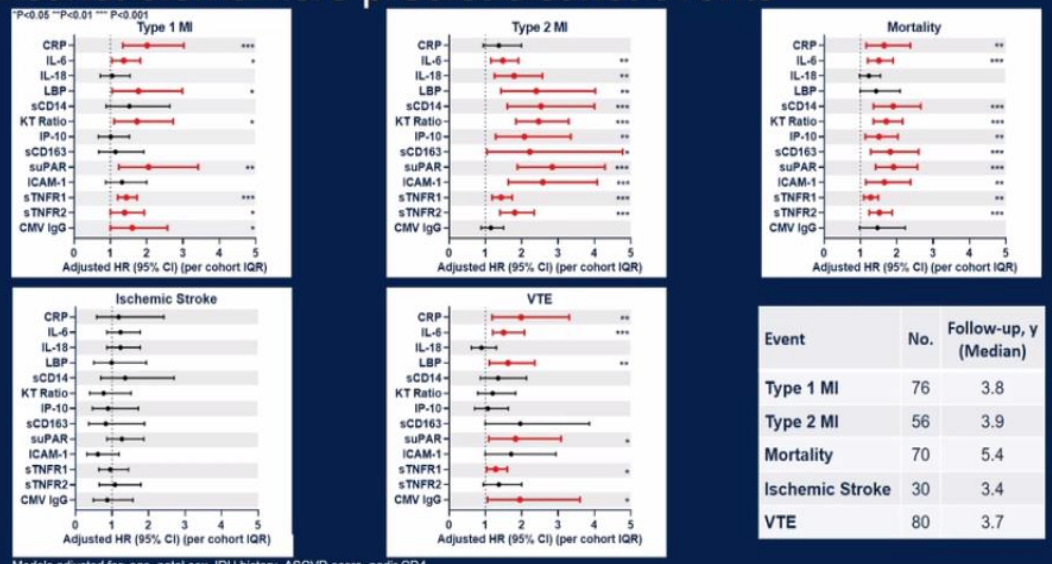


- Case-cohort study within CNICS
  - *Kitahata et al, Int J Epidemiol 2008*
  - Events centrally adjudicated
  - *Crane et al, Am J Epidemiol 2014*
- Inclusion criteria: VL <400 ≥1 year
- Exclusion criteria:
  - Acute infection, hospitalization, or immunosuppressive therapy within 3 months of sample

*All-cause mortality only analyzed in sub-cohort

Characteristics	Median (IQR) or No. (%)
Total participants	979
Age, y	47 (39-53)
Male sex at birth	82%
MSM	63%
IDU history	17%
Smoking history	29%
Diabetes mellitus	13%
ASCVD risk score	4% (2-10%)
CMV IgG+	97%
Current CD4 count	576 (401-807)
Nadir CD4 count	248 (84-410)
VL <400 copies/ml	100%

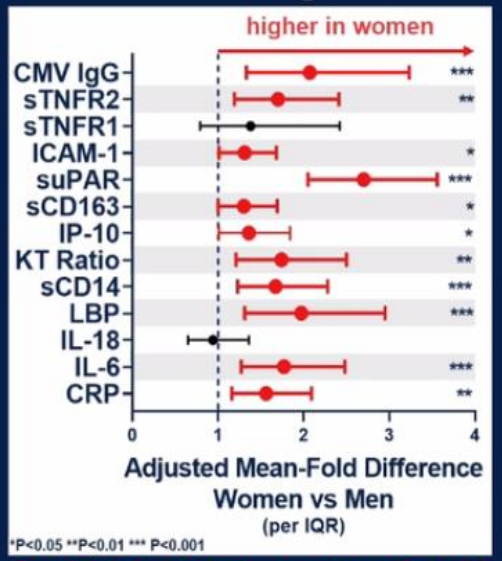
Distinct biomarkers predict distinct events



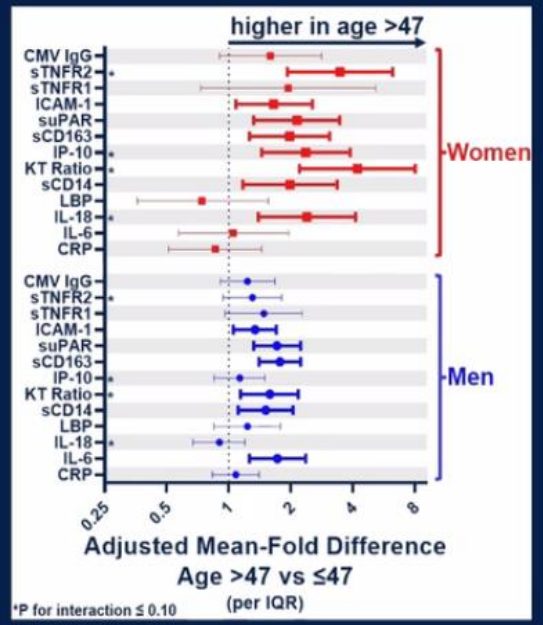
Event	No.	Follow-up, y (Median)
Type 1 MI	76	3.8
Type 2 MI	56	3.9
Mortality	70	5.4
Ischemic Stroke	30	3.4
VTE	80	3.7

- Models adjusted for: age, natal sex, IDU history, ASCVD score, nadir CD4

Women have higher levels of inflammation

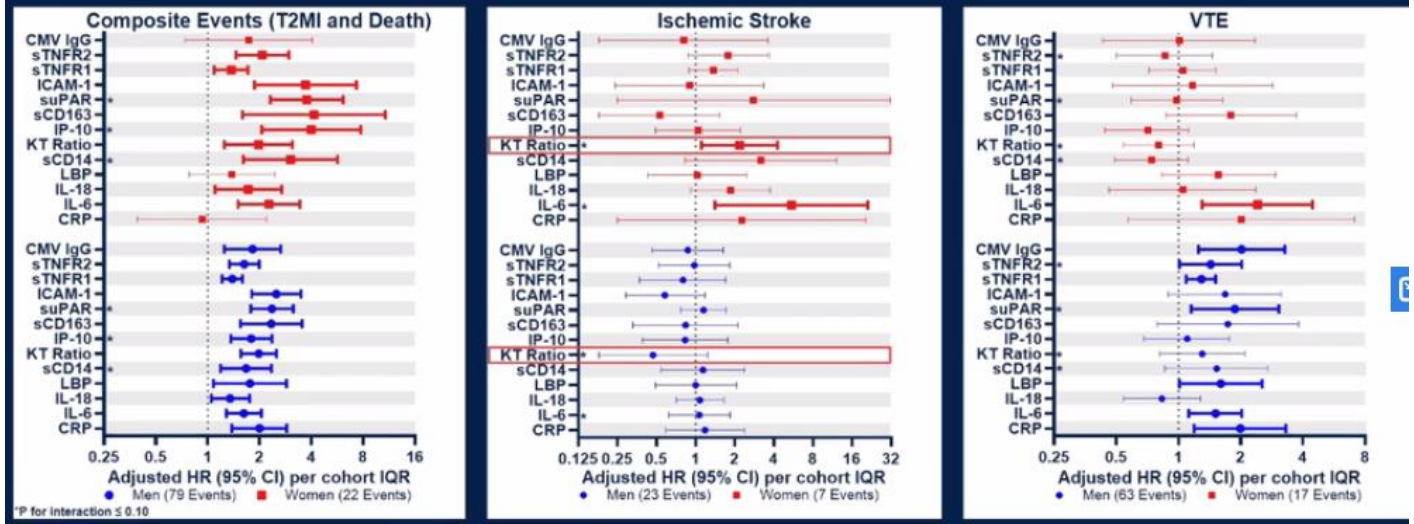


Could this be hormone-mediated?
Median age in cohort: 47



- Models adjusted for: age, natal sex, race/ethnicity, smoking, HCV, IDU history, ASCVD score, nadir CD4, CNICS site

Sex may modify the inflammation-event association



The same increase in immune activation may more strongly predict events in women…

…but may be in a qualitatively different direction for VTE

- Models adjusted for: ASCVD risk score

INSTIs

- AUMENTO de PESO
- RIESGO CARDIOVASCULAR Y DM

CASE-BASED DISCUSSION ON WEIGHT GAIN IN HIV AND ANTIRETROVIRAL THERAPY

PATOGENIA

- Multifactorial: genética, estilo de vida, dieta…
    - No todo es por el TARV
    - Mujer mas riesgo. Mas activación inmune?

- Retorno a la salud
    - Endocrina: *Negative energy balance* con el VIH –TARV repara el efecto negativo y recuperamos peso

- Aumento de apetito. Leptina (saciedad).
    - INSTI podrían actuar aquí? Poca evidencia
- Toxicidad mitocondrial de nuevo? (Dra. McComsey)
    - Biopsia grasa- toxicidad mitocondrial por TDF. Recuperación tras suprimir TDF. Estudios en marcha.
- Fibrosis en la grasa.
    - Inflamación pude relacionarse con fibrosis. Como en obesidad.

TRATAMIENTO

- Cambio de tratamiento?
    - Estudio de *switch*. No optimista sobre volver a NNRTI y perder peso.
- Cambios en estilo de vida cuanto antes.

PREDICTED 10-YEAR RISKS OF CARDIOVASCULAR DISEASE AND DIABETES IN THE ADVANCE TRIAL

Laura Hindley MPH

Study Objective

- This analysis aimed to quantify the 10-year predicted risk of CVD and diabetes for ADVANCE participants using standard risk algorithms

ADVANCE trial design (2017 – 2022)

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

Study visits: Baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96 then every 24 weeks to Week 192
Sample characteristics: 99% black, 56% female, 62% South African

Risk prediction analysis

- Body weight and laboratory measures from Week 144 were used to calculate the 10-year risk of CVD and T2D using the **QRISK**[1], **Framingham**[2] (non-laboratory) and **QDiabetes**[3] risk algorithms
- Participants ≥30 years old at baseline included in analysis
- *Most recent laboratory measure since Week 96 used when Week 144 measure was unavailable

10-year risk of developing:	Heart attack or stroke	Atherosclerotic CVD	Type II diabetes
Risk equation Variables	QRISK3-2018	Framingham (non-laboratory)	QDiabetes-2018
Age (validated population)	✓ (25-84)	✓ (≥30)	✓ (25-84)
Gender	✓	✓	✓
Smoking status	✓	✓	✓
Ethnicity	✓	×	✓
Personal history of CVD	✓	×	✓
Family history of CVD (X)	✓	×	×
Family history of diabetes (X)	×	×	✓
Treatment for hypertension	✓	✓	✓
Prescribed steroids	✓	×	✓
Prescribed statins	×	×	✓
Cholesterol ratio (total cholesterol / HDL)	✓	×	×
Fasting blood glucose (mmol/L)	×	×	✓
Haemoglobin A1C (X)	×	×	✓
Systolic blood pressure (mmHg)	✓	✓	✓
Body mass index (kg/m²)	✓	✓	✓
Other	*	×	*

*Variables marked with **(X)** were not available from the ADVANCE database.*
*Other variables included in QRISK: standard deviation of at least two recent SBP readings (mmHg), erectile dysfunction, atypical antipsychotic medication, history of severe mental, systemic lupus erythematosus, rheumatoid arthritis, migraines, atrial fibrillation, stage 3-5 chronic kidney disease. *Other variables included in QDiabetes: atypical antipsychotic medication, severe mental illness, gestational diabetes and polycystic ovary syndrome.

Summary of risk score changes from baseline to week 144

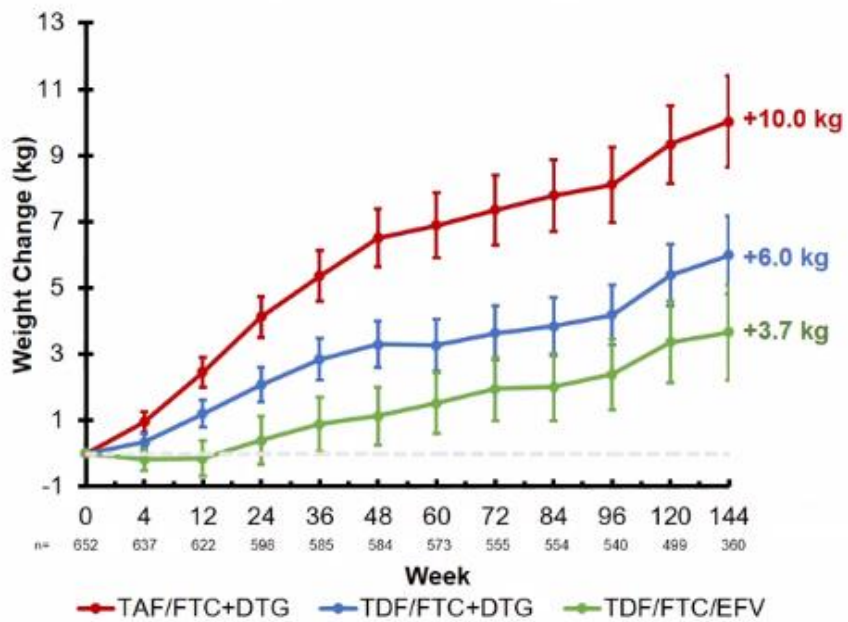
Risk Equation		Arm 1 (TAF/FTC+DTG) n	Arm 1 (TAF/FTC+DTG) Median (Q1, Q3)	Arm 2 (TDF/FTC+DTG) n	Arm 2 (TDF/FTC+DTG) Median (Q1, Q3)	Arm 3 (TDF/FTC/EFV) n	Arm 3 (TDF/FTC/EFV) Median (Q1, Q3)	P-value Arm 1 vs Arm 3	P-value Arm 1 vs Arm 2	P-value Arm 2 vs Arm 3
Framingham (CVD)	Baseline	216	2.63 (1.63, 4.57)	218	2.70 (1.70, 5.42)	215	2.64 (1.60, 4.35)			
	Change to week 144	139	+1.37 (0.56, 2.77)	133	+1.02 (0.38, 2.05)	125	+0.96 (0.46, 2.33)	0.034	0.038	0.982
QRISK (CVD)	Baseline	216	0.60 (0.30, 1.00)	218	0.50 (0.30, 1.10)	215	0.50 (0.30, 1.00)			
	Change to week 144	131	+0.36 (0.14, 0.80)	139	+0.25 (0.10, 0.65)	116	+0.2 (0.10, 0.60)	0.016	0.113	0.377
QDiabetes (T2D)	Baseline	213	0.30 (0.10, 0.70)	210	0.30 (0.10, 1.00)	211	0.30 (0.10, 0.90)			
	Change to week 144	129	+1.50 (0.5, 3.5)	131	+0.80 (0.3, 2.6)	114	+1.25 (0.4, 3.4)	0.674	0.024	0.048

Risk score given as median change (Q1, Q3) in score from baseline. Risk score gives 10-year risk (%) of developing an incident CVD or T2D event. P-values were derived from Mann-Whitney U tests comparing two different treatment groups. All participants ≥30 years old at baseline. The supplementary handout gives risk equation predictions by gender.

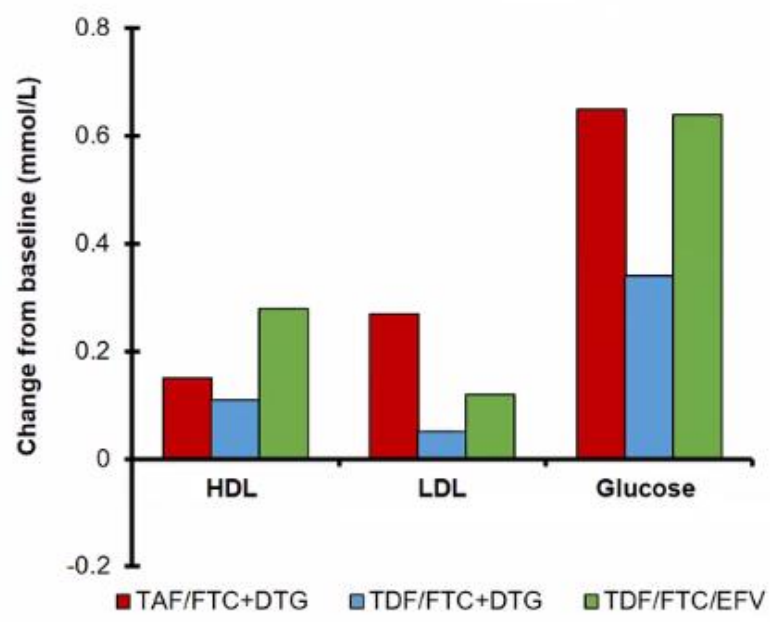
1 additional heart attack or stroke over 10 years per 1000 people treated with TAF/FTC+DTG vs TDF/FTC+EFV (p=0.016, *QRISK*)

7 additional diabetes cases over 10 years per 1000 people treated with TAF/FTC+DTG vs TDF/FTC+DTG (p=0.024, *QDiabetes*)

Weight gain to week 144, participants ≥ 30 years*



Changes in lab parameters to week 144, participants ≥ 30 years**



INCIDENT DIABETES ASSOCIATED WITH INTEGRASE STRAND TRANSFER INHIBITOR INITIATION

Jane O'Halloran
Washington University School of Medicine
St. Louis, Missouri, USA

Primary outcome

New diabetes mellitus or hyperglycemia in the six months post-ART initiation

RESULTS

January 2007 ⟶ June 2018

111,652
initiated ART

34,398 (31%)
INSTI-based regimens

37.7% Raltegravir

35.5% Elvitegravir

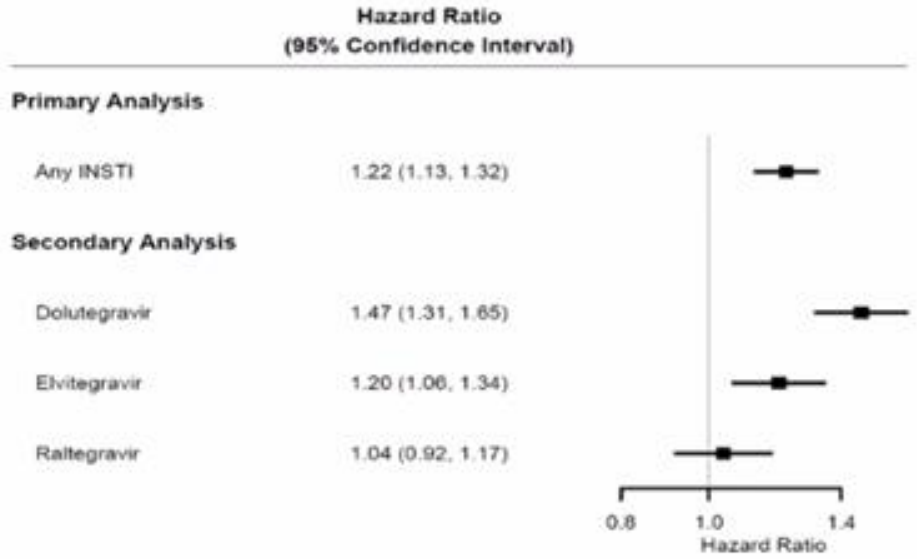
26.8% Dolutegravir

77% of people had a tenofovir disoproxil fumerate containing NRTI backbone

Demographics	INSTI	No INSTI
Mean Age (in years)	42 (12)	43 (10)
Male sex	75%	80%
Medicaid	21%	14%

2,836 (2.5%) event

- 93% new-onset diabetes mellitus, 7% hyperglycemia



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

Limitations

- Administrative data may underestimate rates of hyperglycemia not yet clinically apparent
- Insufficient data to assess the impact of Tenofovir alafenamide

CONCLUSIONS

Overall, those on INSTIs were 22% more likely to develop new-onset diabetes mellitus or hyperglycemia in the six months post index

The risk was more than twice as high in those on dolutegravir compared with those on elvitegravir, while raltegravir was not associated with this finding.

Although analysis on the impact of Tenofovir alafenamide was not performed, it is worth noting that there was almost no TAF use in those receiving dolutegravir

RISK FACTORS FOR PROGRESSION FROM PREDIABETES TO DIABETES IN PERSONS WITH HIV

Mary Clare Masters, MD
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

Study objective

To evaluate risk factors associated with progression from pre-DM to DM in a cohort of older PWH who have been largely virally suppressed and receiving modern ART

Methods

The A5322 (HAILO) Study

Study participants

- AIDS Clinical Trials Group (ACTG) A5322 (HAILO)
  - Ongoing, observational study at 32 U.S. sites
  - Initiated ART through an ACTG randomized clinical trial
  - Undergo annual fasting laboratory tests

Definitions

- Pre-DM: fasting blood glucose (FBG) of 100-125 mg/dl
- DM: FBG≥126 mg/dl, receiving medication treatment for diabetes, or clinical diagnosis

Data analysis

- Proportional hazards Cox regression models to identify risk factors for development of DM among participants with pre-DM
- Factors associated with DM in univariable models (p-value <0.10) were included in multivariable model

Results

1035 HAILO participants
- 60 (6%) with DM at baseline
- 74 (7%) with pre-DM at baseline
- 679 (66%) developed pre-DM during follow-up

Table 1. Participant characteristics at diagnosis of pre-DM

Characteristics	Total (N=753)	Developed DM (N=167)
Age in years	46 (41, 51)	45 (39, 50)
Female sex	121 (16.1%)	28 (16.8%)
Race/ethnicity		
Black, non-Hispanic	214 (28.4%)	45 (26.9%)
White, non-Hispanic	376 (49.9%)	83 (49.7%)
Other + Hispanic	163 (21.6%)	39 (23.4%)
HIV-1 RNA <50 (copies/ml)	552 (73.3%)	107 (64.1%)
CD4 counts (cells/mm^3) >200	665 (88.3%)	132 (79.0%)
BMI (kg/m^2)	26.6 (24.1, 30.5)	28.0 (24.6, 31.3)
Waist circumference (cm)	93.5 (86.0, 102.4)	95.8 (88.7, 106.9)
INSTI use	93 (12.4%)	3 (1.8%)

Table 2. Risk of DM in persons with pre-DM: Multivariable model

Variable	HR	95% CI	p-value
Clinical site region (ref=West)			
Northeast	**1.68**	**1.09, 2.61**	**0.02**
Midwest	1.40	0.91, 2.16	0.13
South	1.19	0.72, 1.95	0.50
HIV-1 RNA <50 (copies/ml)	0.95	0.68, 1.32	0.74
CD4 counts (cells/mm^3) >200	**0.55**	**0.37, 0.81**	**<0.01**
INSTI use	**0.21**	**0.07, 0.67**	**<0.01**
BMI, per 1-unit increase	**1.05**	**1.02, 1.08**	**<0.01**
History of hypertension	1.24	0.87, 1.77	0.24
Family history of CVD	0.83	0.53, 1.28	0.40

- Of those on an INSTI, 67% were on raltegravir, 18% dolutegravir, 12% elvitegravir, and 3% bictegravir
- Median (IQR) time to DM was 45.3 weeks (18.7, 58.6)

- While INSTI use has been associated with weight gain and DM in other cohorts, its use was associated with a *lower* risk of progression to DM among HAILO participants.
- Higher CD4 was also associated with a lower risk of progression to DM, suggesting that immunosenescence as well as inflammation may be mediators in DM development among PWH with pre-DM.
- Further characterization of the metabolic effects associated with INSTI use and the effects of immune activation and inflammation on development of DM in PWH are needed.

ASSOCIATION BETWEEN INTEGRASE STRAND TRANSFER INHIBITORS AND CARDIOVASCULAR DISEASE

Bastian Neesgaard *on behalf of the RESPOND study group*
CHIP, Dept. of Infectious Diseases Section 2100, Rigshospitalet, Copenhagen, Denmark

Study objectives:

- To assess if exposure to INSTIs* (raltegravir [RAL], elvitegravir [EVG/c] and dolutegravir [DTG]), is associated with an increased incidence of CVD.

Methods:

RESPOND International Cohort Consortium of Infectious Diseases

Inclusion:

- INSTI naïve RESPOND participants [1-2] aged ≥18 years, followed from latest of cohort enrolment or 1st of January 2012 (baseline)

Outcomes:

- CVD - composite endpoint consisting of rigorously defined myocardial infarction (MI), strokes, and invasive cardiovascular procedures (ICP)

Statistical analysis:

- Individuals were followed from baseline to the earliest of first CVD event, last follow-up or 1st of october 2018.
- Exposure to INSTIs was calculated following the methodology developed in D:A:D study. [3]
- Negative binomial regression models, adjusted for common CVD risk factors, HIV characteristics and ARVs previously associated with CVD - factors potentially associated with INSTI use and CVD were fixed at baseline.
- Logistic regression examined odds of starting an INSTI by D:A:D 5-year CVD risk score.

Results:

- A total of **21,267** participants were included; **9,782 (46%)** exposed to an INSTI during follow-up. (**6372** to DTG**, 2385** to EVG/c and **2147** to RAL)
- Overall, **75.5% were white, 73.3% male, 48.9% of Western European origin** and **41.2% MSM.**
- During a **median of 6.3 years** of follow-up (IQR 3.5-6.7; 106,870 PYFU); **517** CVD events (**IR 4.9/1000 PYFU** [CI 95%, 4.5-5.3]) of which, **210 MIs, 162 strokes** and **145 ICPs.**
- Individuals experiencing CVD were older (**median**, [IQR]: **53.7** [48.5-61.9] vs. **44.5** [36.2-51.5] years), and a larger proportion had classic risk factors for CVD at baseline, than those without.
  - Greater proportion with a high/very high **5-year estimated D:A:D CVD risk score** in the group that experienced CVD (**46% vs 12%, P<0.001**).
- **Odds ratio*** [95%CI] of initiation INSTI by 5-year estimated D:A:D CVD risk, when compared to all compared to low risk (<1%):
  - Moderate risk (1 - <5%): **1.11** [1.00-1.21], high risk (5 - <10%): **1.19** [1.05-1.35], very high risk (>10%): **1.05** [0.89-1.25].

Results:

Figure A:
Crude incidence rates of CVD stratified by INSTI exposure

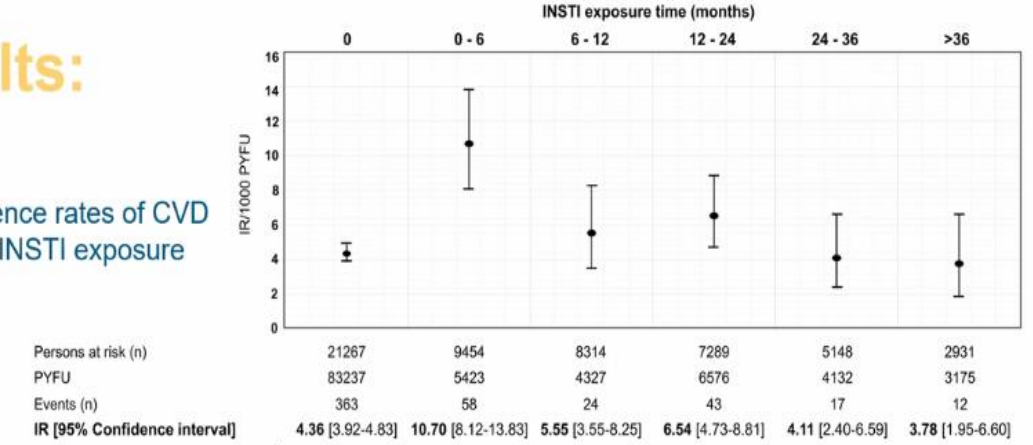
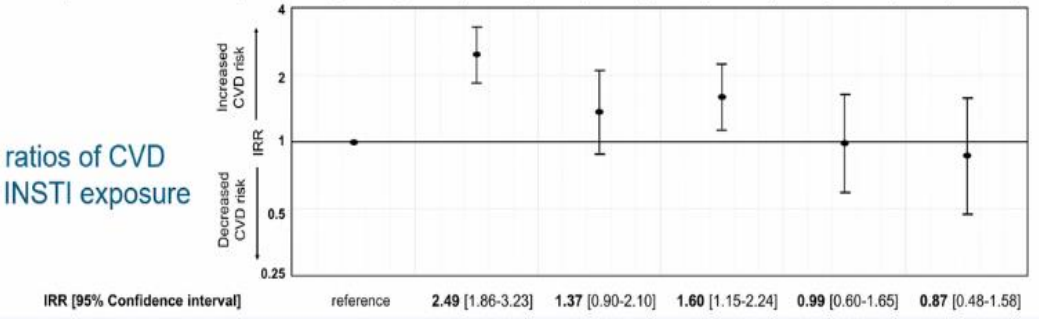


Figure B:
Adjusted IR ratios of CVD stratified by INSTI exposure



Conclusion:

- The INSTIs examined were associated with a 2.5 times greater incidence of CVD in the first 6 months of exposure when compared to no INSTI exposure, after accounting for known CVD risk factors, and across a wide range of sensitivity analyses.
- These findings call for further investigations in mechanistic studies and other large populations of people living with HIV seen in routine clinical care.

ENVEJECIMIENTO

PREVALENCE AND DETERMINANTS OF FRAILTY IN PLHIV AGED 70+: ANRS SEPTAVIH STUDY

- The objectives of this study were to assess the prevalence of frailty in PLHIV aged 70+, using the Fried phenotype index and to evaluate the association of frailty with HIV and non HIV-related factors.

METHODS

- **SEPTAVIH ANRS EP66** study is a French, multicenter, prospective, observational study.
- Main Inclusion criteria: HIV-1 infection, aged 70 or older, ART treated for at least 12 months
- At baseline, we collected the following data:
  - Sociodemographic, clinical data and medical/HIV history
  - A comprehensive geriatric interview and examination assessing
    - history and risks of falls
    - associated medications
    - physical and cognitive function (MoCA)
    - mood disorders (CES-D questionnaire)
- Frailty was assessed using the 5 Fried frailty phenotype (FFP) criteria: recent spontaneous weight loss, low handgrip strength, exhaustion, slow walking speed, low physical activity.

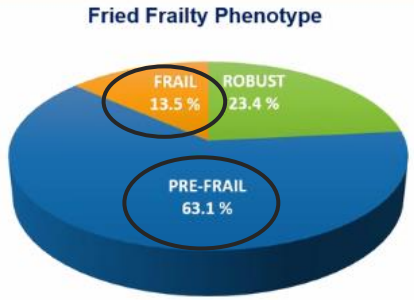
PLHIV were categorized as **robust** (no criteria), **pre-frail** (1 or 2 criteria) and **frail** (> 2 criteria).

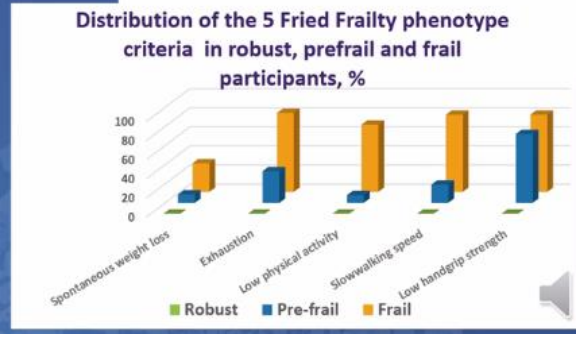
- We compared the frailty categories at baseline according to HIV parameters and socio-demographic factors (continuous variables with Kruskal-Wallis tests and categorical variables using Chi-2 tests).

Characteristics of the Frailty phenotype in PLHIV 70+: the ANRS SEPTAVIH Study

From May 2019 to Jan 2020 **510 PLHIV** were included

- Age (med.) 73 years [IQR:71-77]
- Male 81.4 % (MSM 58.1 %)
- History of clinical AIDS 27.4%
- Known HIV duration (med.) 22.7 years
- Plasma HIV RNA <50 c/mL 95.3 %
- Baseline CD4 cell count (/mL) 562 [418-752]
- Non communicable comorbidities 3 [2-4]





Factors associated with Frailty in PLHIV 70+: the ANRS SEPTAVIH Study

% or median	Robust n=111, 23.4%	Pre-frail n=300, 63.1%	Frail n=64, 13.5%	P-value
Age, years	**72**	**73**	**76**	**<0.001**
Male	79.3	82.3	73.4	0.85
College education level	**48.6**	**36.3**	**35.9**	**0.02**
Homeowner	**70.3**	**60.0**	**45.3**	**0.03**
Baseline CD4/mL	623	565	498	0.05
Nadir CD4/mL	185	187	155	0.53
HIV-RNA≤50c/mL at baseline	96.4	94.3	85.9	0.42
Duration of HIV infection, years	22.5	22.8	23.3	0.84
Comorbidities	**2**	**3**	**3**	**0.04**
Deprived socioeconomic status	**20.7**	**32.7**	**48.4**	**<0.001**
Cognitive impairement	**44.1**	**63.3**	**60.9**	**<0.001**

- In this population aged 70 or older, with a long duration of HIV infection, on ART and virologically suppressed, the prevalence of frailty was low, though nearly two thirds were prefrail.
- Socio-economic conditions, comorbidities and cognitive function were strongly associated with frailty, while HIV-related factors were not.
- These results suggest the need of targeted interventions in aging PLHIV to screen, prevent and manage frailty.

COMORBILIDADES

Multimorbidity in people with HIV using ART in the United States: Projections to 2030

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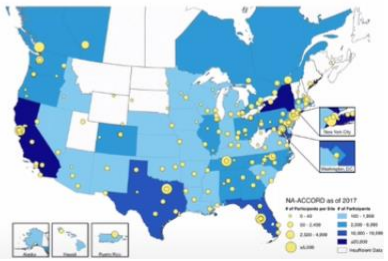
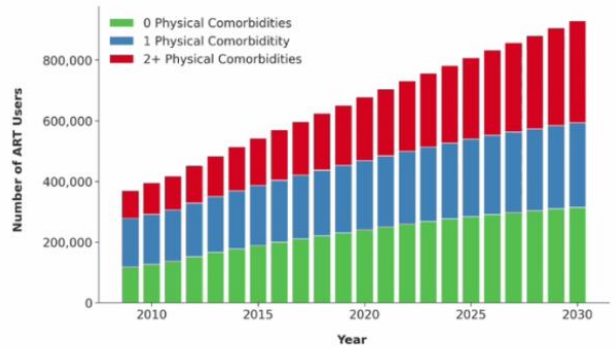
PEARL unique characteristics

- Embraces the diversity of people with HIV
  - 5 gender and HIV acquisition risk groups * 3 races and ethnicities = **15 subgroups**
- Leverages the breadth of the **CDC Surveillance** data, and the depth of the longitudinal **NA-ACCORD** data
- Simulating the US adult population age 15 to 85 **who have ever started ART**



Projected burden of multimorbidity among people with HIV using ART in the US, 2009 – 2030



Population with with ≥2 physical comorbidities in addition to HIV in:

2020:
30% (678,000 persons)

2030:
36% (929,000 persons)

~251,000 additional individuals living with ≥2 physical comorbidities

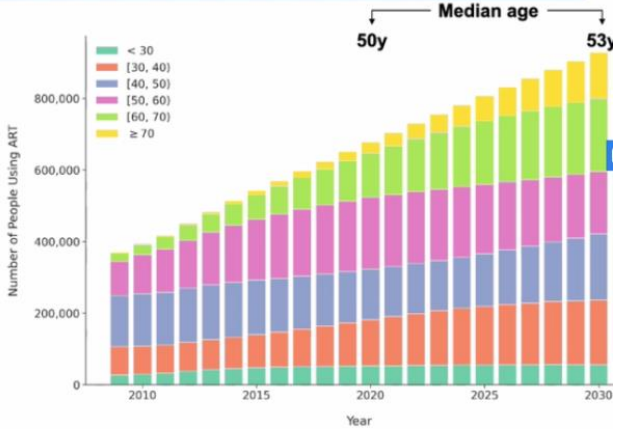
Hypertension, Hyperlipidemia, Diabetes, CKD, Cancer, MI & ESLD

PEARL model

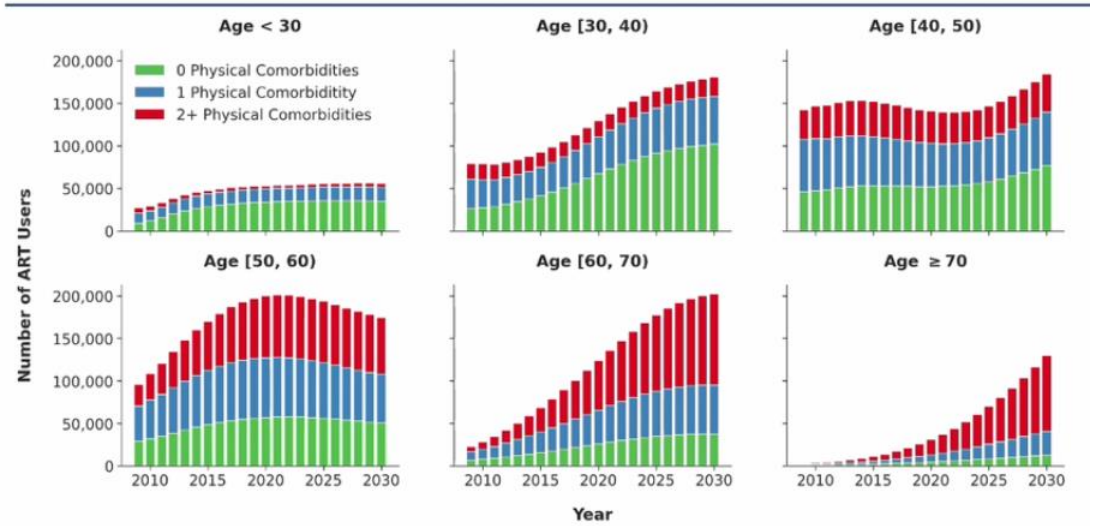
ProjEcting Age, multimoRbidity, and poLypharmacy

Results

- PEARL projects a substantial increase in number of ART users, reaching a population of 928,000 by 2030
- The overall median age increased from 50y in 2020 to 53y in 2030, with 25% of ART users ≥65y in 2030

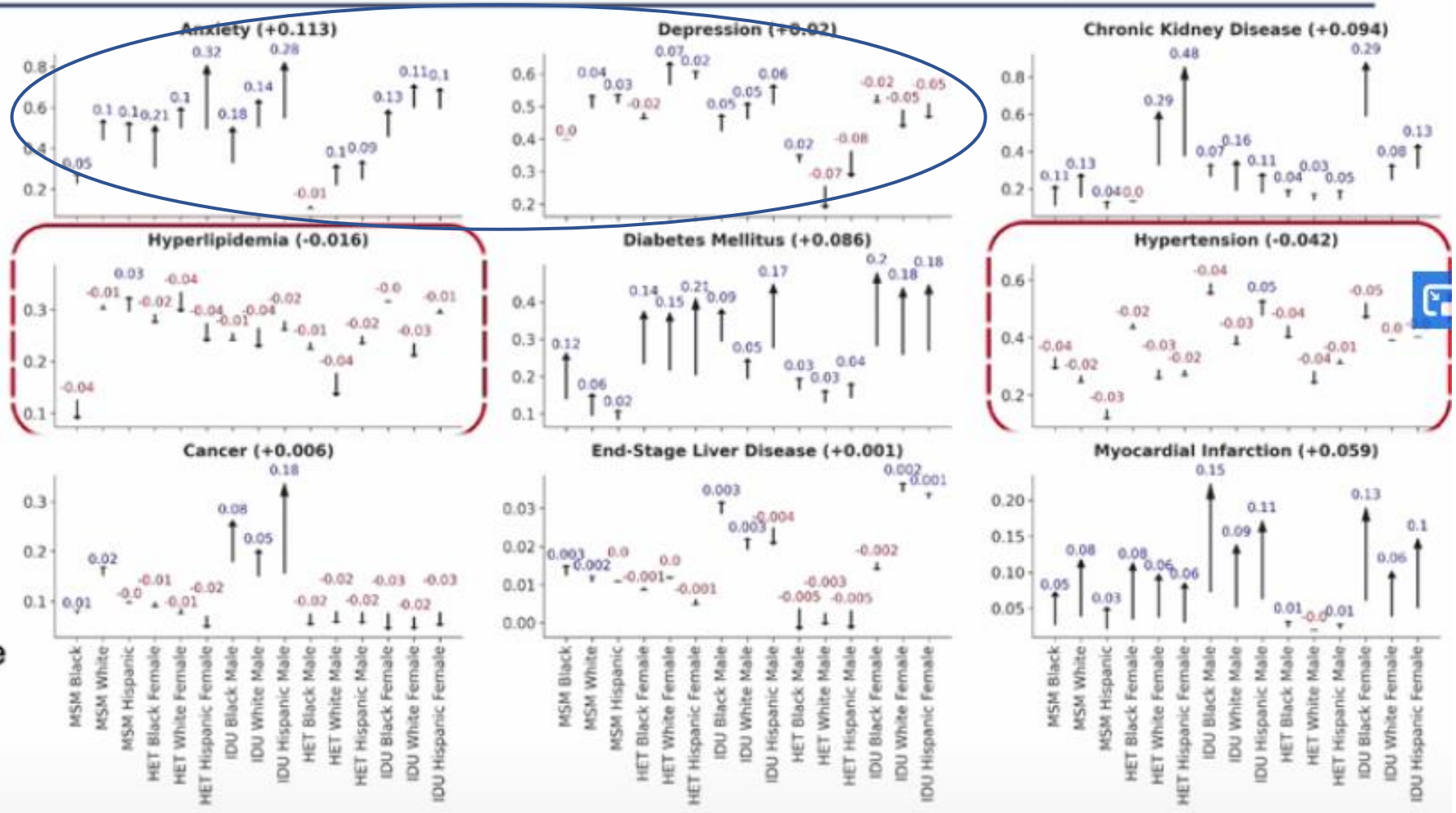


Projected burden of multimorbidity by age



Projected change in prevalence of comorbidities among people with HIV using ART in the US, 2020 – 2030

- Projected increase in prevalence of Anxiety, CKD, Depression, Diabetes & MI
- Projected slight reductions in prevalence of hyperlipidemia & hypertension
- Projected rise in cancer among male IDUs



COMORBIDITY BURDEN IN PEOPLE LIVING WITH HIV IN THE UNITED STATES

Patient Characteristics

20,256 PLWH were matched to **40,512** PLWoH

- 62% ≥50 years old
  Mean (SD): 52.3 (14.5) years
- 20.0% Female
- 45.9% White; 28.5% Black; 13.8% Hispanic
- 59.1% from South Region of US
- 65.4% Commercial insured
  34.6% Medicare Advantage

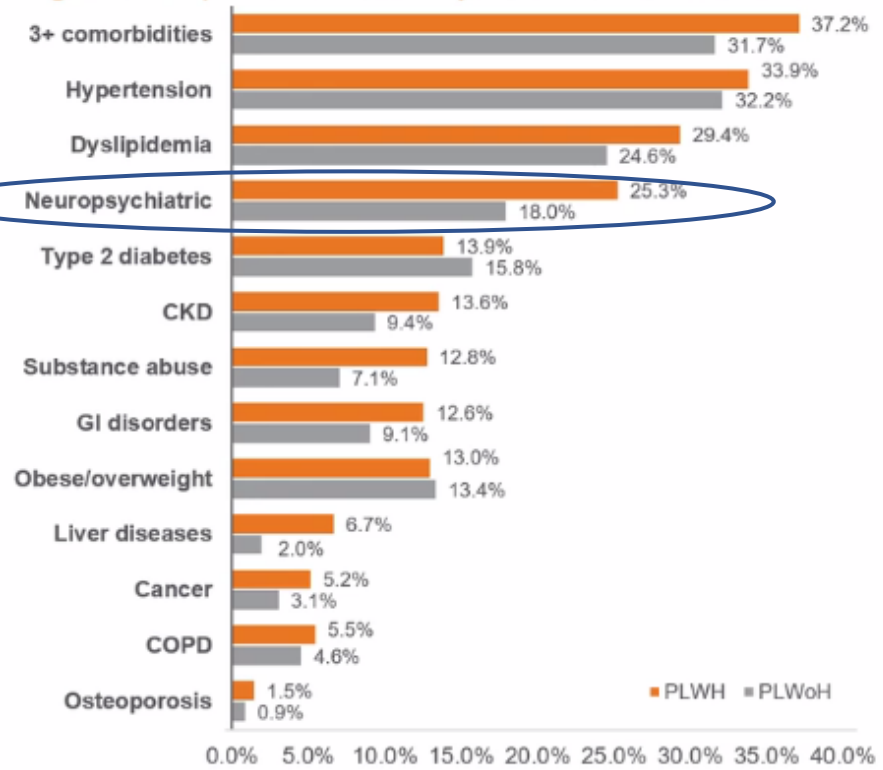
Table 1. Comorbidity Index Scores*

CCI score	PLWH (n=20,256)	PLWoH (n=40,512)
mean (SD)	0.9 (1.6)	0.6 (1.3)
Categories, %		
0	61.3%	72.1%
1	14.1%	12.1%
2	12.0%	8.1%
3-4	8.1%	5.3%
≥5	4.5%	2.4%

*All p<0.001.

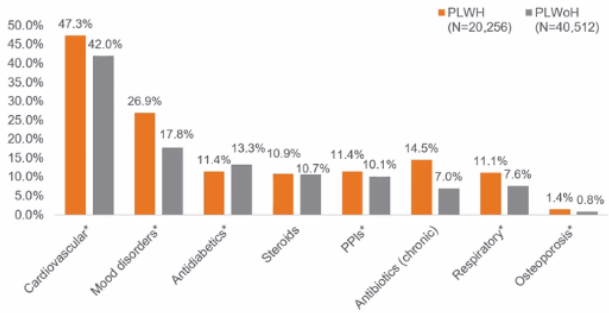
CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; GI: gastrointestinal; PLWH: people living with HIV; PLWoH: people living without HIV; SD: standard deviation

Figure 1. Comparison of Comorbidity Burden in PLWH and PLWoH



Note. All p<0.001 except obesity/overweight: p=0.206

Figure 2. Types of medications



*p<0.001.

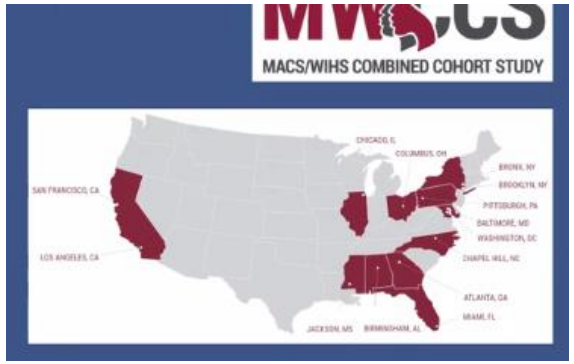
Table 2. Co-medication burden (non-ART)

Polypharmacy*	PLWH (n=20,256)	PLWoH (n=40,512)
Mean (SD) unique NDCs	11.9 (10.1)	9.2 (9.4)
0 unique fills, n (%)	157 (0.8)	3,001 (7.4)
1 unique fill, n (%)	1,051 (5.2)	3,878 (9.6)
2 unique fills, n (%)	1,159 (5.7)	3,277 (8.1)
3 unique fills, n (%)	1,213 (6.0)	2,990 (7.4)
4 unique fills, n (%)	1,221 (6.0)	2,727 (6.7)
≥ 5 unique fills, n (%)	15,445 (76.3)	24,639 (60.8)

*p<0.001.

ART: antiretroviral therapy; NDC: National Drug Code; PLWH: people living with HIV; PLWoH: people living without HIV; PPI: proton pump inhibitors; SD: standard deviation

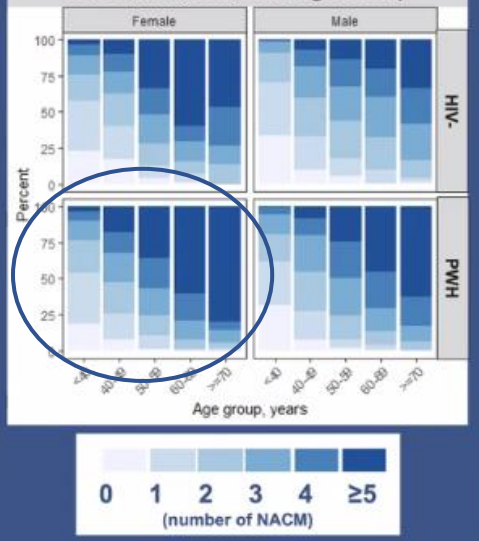
HIV DIFFERENTIALLY IMPACTS AGE-RELATED COMORBIDITY BURDEN AMONG US WOMEN AND MEN



Characteristics at End of Observation	Women (n=3238)	Men (n=2691)
Median age, *yrs*	51	58
Median BMI, *kg/m²*	30	26
Black race	65%	25%
Income <150% FPL	78%	32%
Ever smoking	68%	70%
	Women with HIV (n=2316)	**Men with HIV (n=1452)**
Median CD4, *cells/mm³*	620	636
HIV-1 RNA <200 cp/ml	81%	86%
Median time since ART initiation, *yrs*	12.9	15.4

BMI=body mass index; ART = antiretroviral therapy; CVD = cardiovascular disease; FPL = federal poverty level

Prevalent Comorbidity Burden by HIV Serostatus, Sex, and Age Group

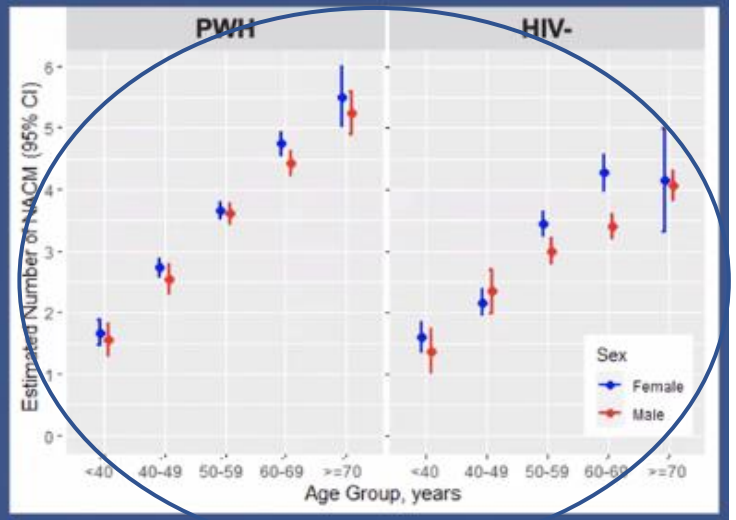


NACM prevalence	Women	Men
Hypertension	68%	75%
Psych illness	55%	58%
Dyslipidemia	41%	64%
Liver disease	34%	38%
Bone disease	42%	19%
Lung disease	38%	10%
Diabetes	24%	17%
CVD	15%	15%
Kidney disease	14%	15%
Cancer	7%	12%

Median NACM burden among women vs men: 3.4 vs 3.2, *p*=0.015

Estimated Mean Difference in NACM burden†				
Women *vs* men	**PWH**		**HIV-**	
<40 yrs	+0.33	*p*=0.03	+0.52	*p*=0.01
40-49 yrs	+0.37	*p*<0.01	-0.07	*p*=0.72
50-59 yrs	+0.38	*p*<0.01	+0.88	*p*<0.01
60-69 yrs	+0.66	*p*<0.01	+1.39	*p*<0.01
≥70 yrs	+0.62	*p*=0.03	+0.33	*p*=0.46

†Unadjusted linear regression model including HIV, age, sex and all interaction terms in the model: HIV*age *p*=0.0002, HIV*sex *p*=0.3040, age*sex *p*<0.0001, HIV*age*sex *p*=0.0014



In the adjusted model†, findings were attenuated but HIV and age still significantly modified the estimated mean NACM burden by sex (HIV*age*sex, *p*=0.038)

†Including covariates in the unadjusted linear regression model plus race, body mass index, smoking, drinking, cocaine, socioeconomic status

CONCLUSIONS

- The prevalence and burden of NACM was high in the MWCCS among men and women with or at-risk for HIV
  - Particularly for hypertension, psychiatric illness, dyslipidemia, liver, and bone disease
- NACM burden was higher among women vs men, particularly among PWH, and varied by age category
  - The distribution of specific NACM prevalence differed by sex
- Given HIV is associated with differential effects on age-related comorbidities by sex, HIV serostatus- and sex-specific strategies for NACM screening and prevention are needed

¡MUCHAS GRACIAS!

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