# Envejecimiento y comorbilidades

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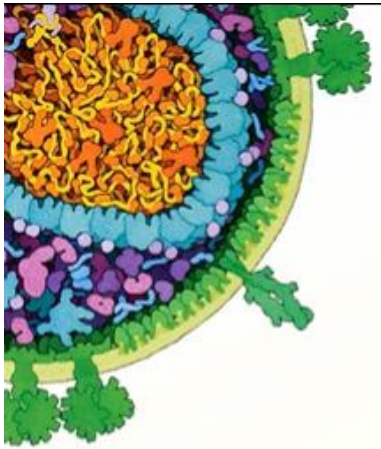
Fundació Lluita contra les Infeccions

## 30 años CROI
## 20 años PostCROI

# 1.
# NAFLD / NASH / Liver fibrosis



THEMED DISCUSSION: TD-02

Monday, February 20, 2023

# PREVALENCE AND FACTORS ASSOCIATED WITH NAFLD IN PEOPLE WITH HIV

**Louise E. van Eekeren**

*Radboud University Medical Center, Nijmegen, Netherlands*

30th CROI 2023

Disclosure(s): ViiV Healthcare: Grants/grants pending (Ongoing)

## Aims

1) Determine the prevalence of liver steatosis and fibrosis

2) Assess associations between steatosis and fibrosis, and demographic-, metabolic-, and HIV-specific factors, including ART regimens

## Methods

- 2000HIV cohort
- FibroScan®:
  - Liver stiffness measurements (LSM)
  - Controlled attenuation parameter (CAP)

# Overview of the study

**Inclusion**
- HIV-1
- ≥ 6 months ART
- VL < 200 copies/mL

**Exclusion:**
- Active HBV/HCV
- Other active infection
- Pregnancy

| | |
|---|---|
| Age (years) | 52.0 [43.0 – 59.0] |
| Sex (males) | 86.6% |
| BMI (kg/m²) | 25.1 [22.6 – 27.8] |
| Ethnicity (white) | 82.1% |
| T2DM | 5.2% |
| HIV duration (years) | 11.0 [5.9 – 16.6] |
| HIV transmission (MSM) | 74.8% |
| CD4 nadir ($10^6$ cells/L) | 270 [150 – 400] |

Total population: n = 1895

FibroScan: n = 1109

Excluded: n = 34

Valid LSM and/or CAP result: N = 1075

# Prevalence of liver steatosis and fibrosis

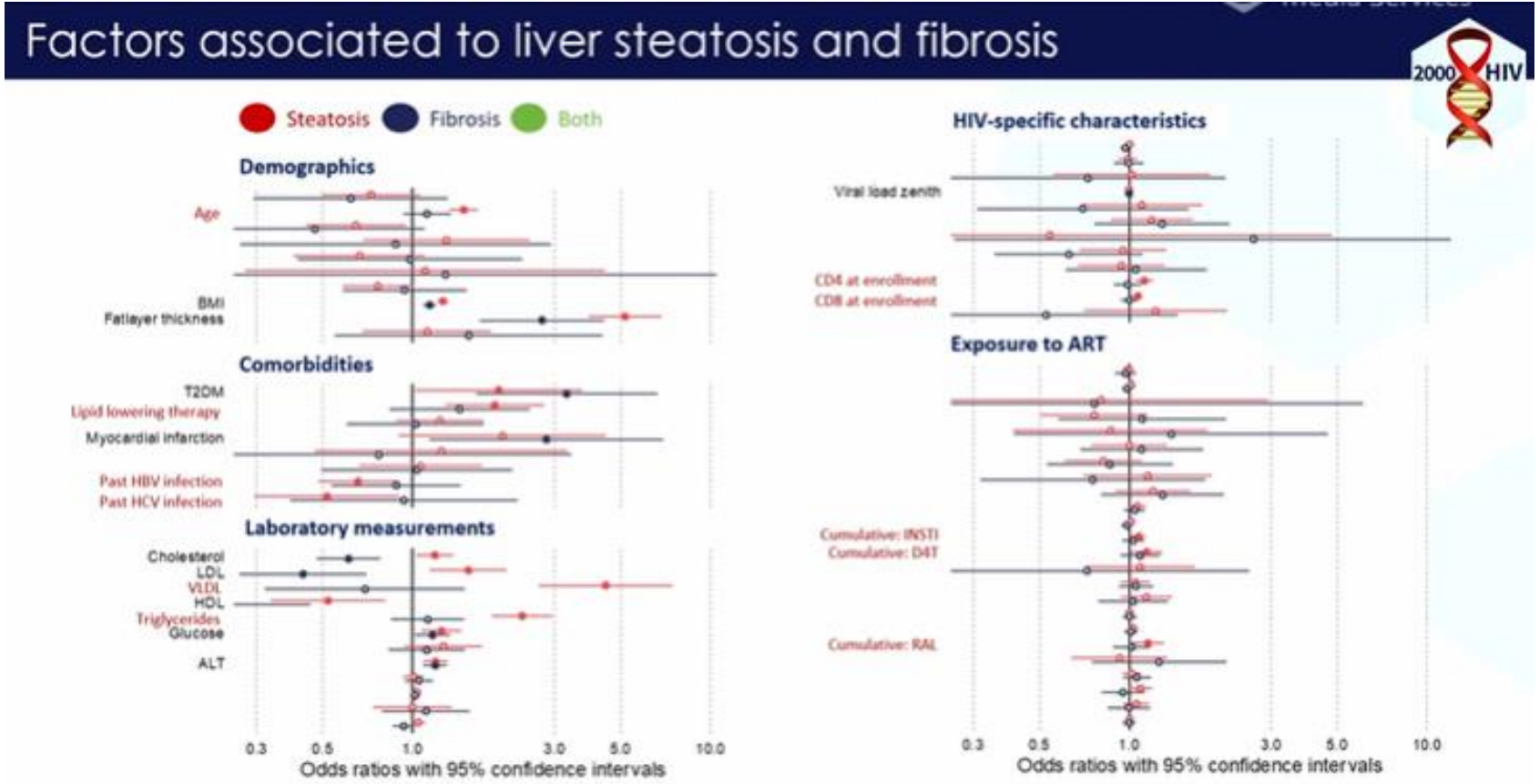
**Steatosis**
CAP ≥ 248 dB/m

47.5% steatosis


**Fibrosis**
LSM ≥ 7.0 kPa

8.8% fibrosis

# Factors associated to liver steatosis and fibrosis



# Discussion

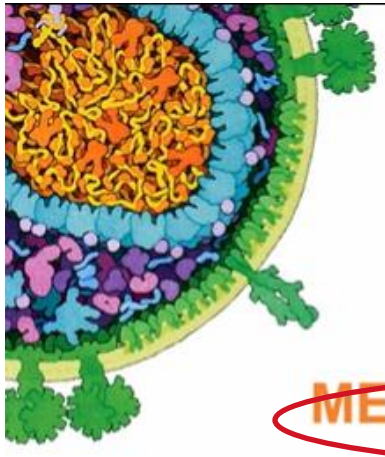
Liver steatosis and fibrosis affect nearly one in two and one in ten PLHIV.

47.5% steatosis  8.8% fibrosis

NAFLD was most strongly associated with metabolic risk factors → focus on metabolic alterations that may contribute to NAFLD.

ART: cumulative duration of treatment with INSTI may increase risk of NAFLD → mediated by weight gain?

High CD4+ and CD8+ T cell counts at enrollment are associated with liver steatosis → further elucidate role of adaptive immunity in NAFLD.



THEMED DISCUSSION: TD-02

Monday, February 20, 2023

# SEX DIFFERENCES IN THE ASSOCIATION OF HIV WITH METABOLIC-FATTY LIVER DISEASE


**Dana Kablawi**

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30th CROI 2023

Disclosure(s): No financial relationships to disclose

**Objective:** ***Investigate sex differences in the incidence and prevalence of MAFLD and liver fibrosis in HIV population***

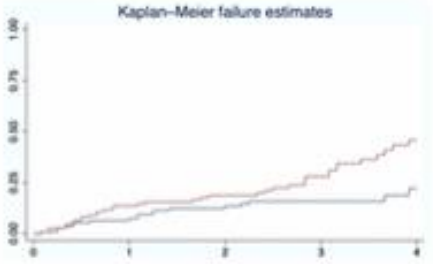

| Population characteristics (N= 1359) | |
|---|---|
| Age | 51.8 |
| Female | 25% |
| BMI | 25.1 |
| Ethnicity | 25% black, 64% white |
| HIV duration | 17.2 (9.5) years<br>30% HCV co-infected |

- Multicenter cohort study of consecutive PWH who underwent screening for MAFLD and liver fibrosis by liver stiffness measurement with associated CAP
- MAFLD was defined as:
  - Presence of hepatic steatosis (CAP≥270 dB/m) plus any among type 2 diabetes, overweight (BMI>25 Kg/m$^2$) or two other metabolic abnormalities
- Significant liver fibrosis was diagnosed as LSM≥8 kPa
- The incidence of MAFLD and significant liver fibrosis was assessed through survival analysis

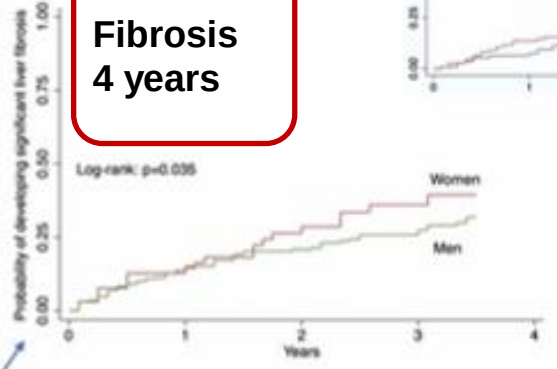
# Results

## Baseline characteristics

| | Female | Male |
|---|---|---|
| Prevalence of MAFLD | 17.7% | 24.3% |
| Prevalence of liver fibrosis | 10.7% | 13.4% |
| Black ethnicity | 48% | 17% |
| ALT, U/L | 26.4 ± 20.4 | 33.4 ± 22.5 |
| HDL cholesterol, mmol/l | 1.46 ± 0.57 | 1.11 ± 0.33 |
| Triglycerides, mmol/l | 1.69 ± 0.96 | 2.47 ± 2.63 |

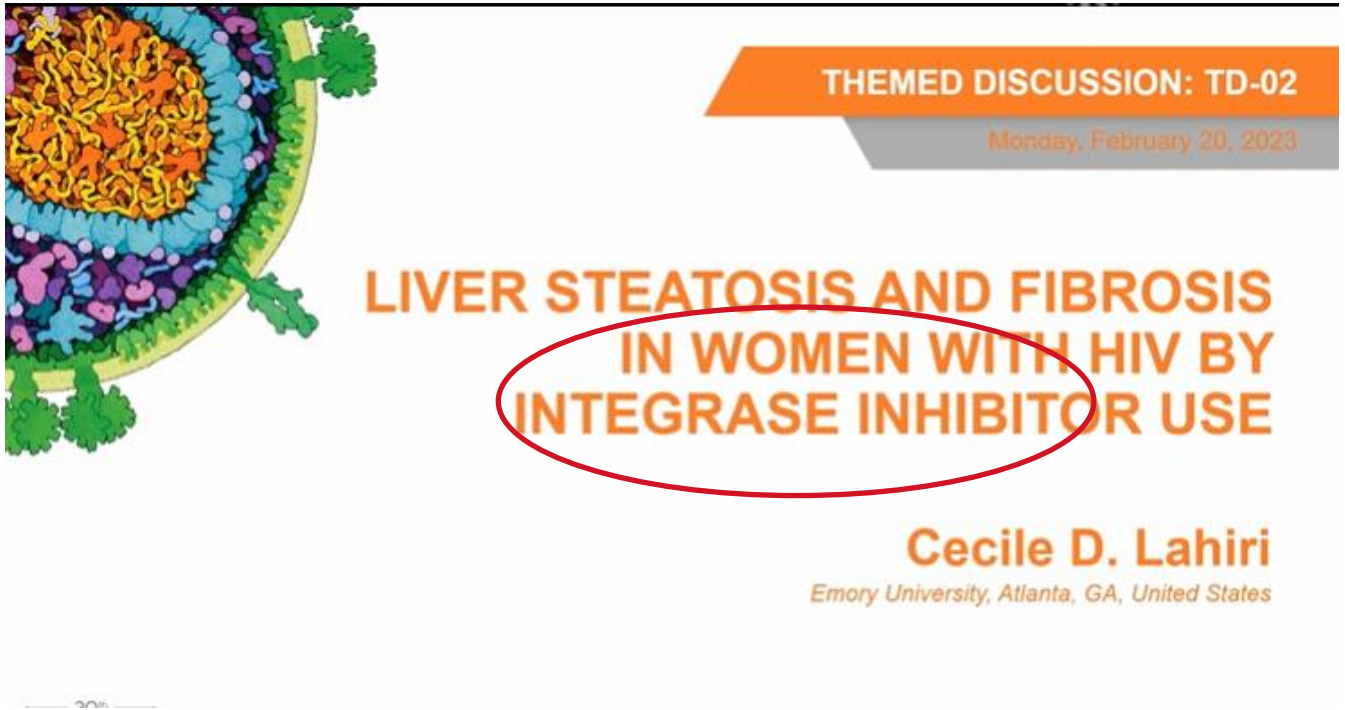



**Fibrosis 4 years**



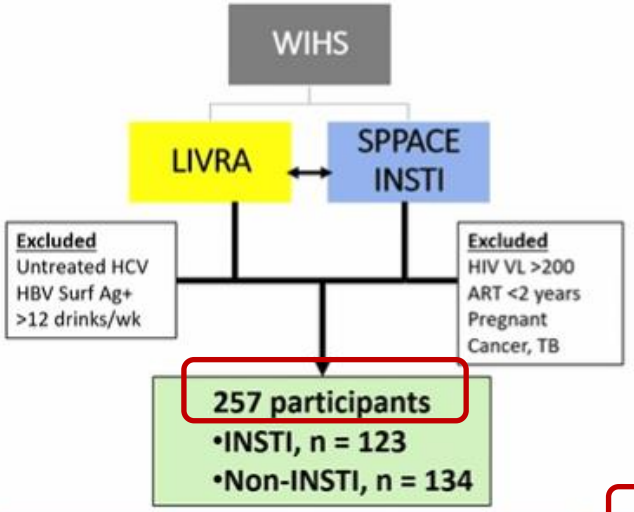

- Incidence of **MAFLD similar between women and men with HIV**
- Incidence of **liver fibrosis was higher in women** vs. men with HIV
  - 7.0 vs. 5.9 per 100 PY particularly **after 50 years old**

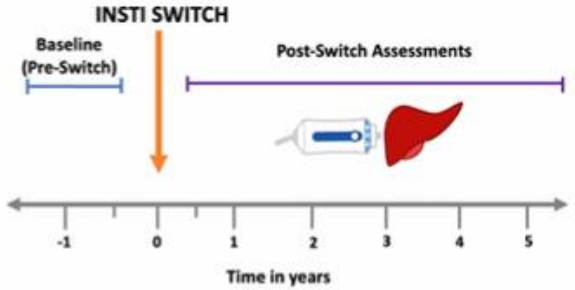
- On multivariable cox regression and after age adjustment: **MAFLD** (aHR 3.3, 95% CI 2.0-5.6) **and female sex** (aHR 2.2, 95% CI 1.3-3.5) **were independent predictors** of developing significant liver fibrosis while **CD4 cell count was protective** (aHR 0.99, 95% CI 0.99-0.99).


THEMED DISCUSSION: TD-02
Monday, February 20, 2023
LIVER STEATOSIS AND FIBROSIS IN WOMEN WITH HIV BY INTEGRASE INHIBITOR USE
Cecile D. Lahiri
Emory University, Atlanta, GA, United States

## STUDY AIM

Assess **hepatic steatosis** and **fibrosis** among **women with HIV** switching to INSTIs vs those on non-INSTIs


### Outcomes

- **Liver steatosis (CAP)** = controlled attenuation parameter (≥ 248 dB/m)
- **Liver stiffness (LS)** = shear wave elastography (≥7.1 kPa)
- **FibroScan AST (FAST) Score** ≥ 0.67

### Analyses

- Mixed-effects and logistic regression models for continuous and categorical outcomes, respectively
- **Adjusted for**: Age, CD4%, BMI, TDF or TAF use,

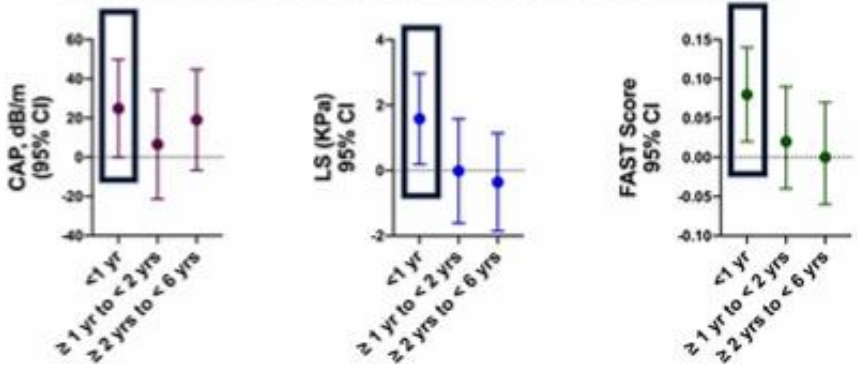
# Results

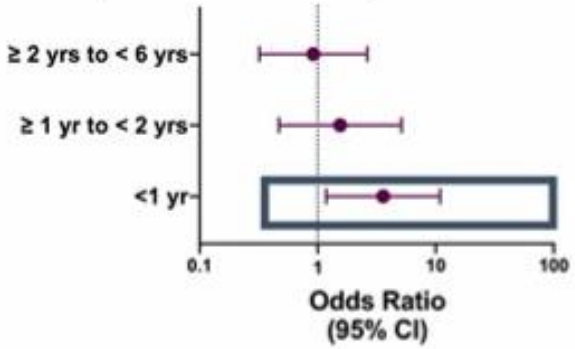
| Cohort Characteristics (time of FibroScan) | | |
|---|---|---|
| **Mean (SD), median (Q1, Q3) or n(%)** | **INSTI N=123** | **Non-INSTI N=134** |
| **Age, yrs** | 50 (8) | 49 (8) |
| **Black race** | 82 (67) | 107 (80) |
| **Alcohol use** | | |
| Abstainer | 75 (62) | 84 (63) |
| 1-7/wk | 44 (36) | 49 (37) |
| **CD4, cells/mm³** | 836 (316) | 758 (290) |
| **CD4 nadir** | 214 (87, 344) | 245 (141, 360) |
| **NRTI** | | |
| **TDF*** | 28 (23) | 109 (81) |
| **TAF*** | 51 (42) | 15 (11) |
| **ABC*** | 33 (27) | 10 (8) |
| **BMI, kg/m²** | 32 (8) | 32 (8) |

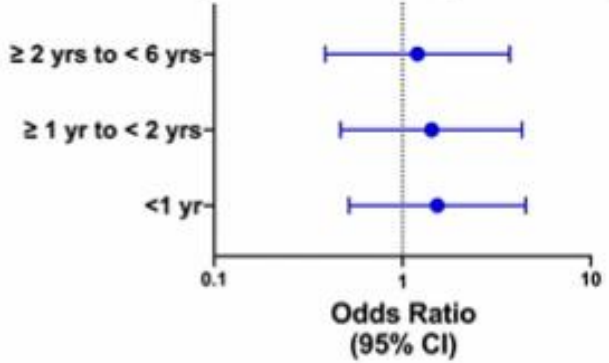
## Change from pre-switch to Fibroscan

| | INSTI | Non-INSTI |
|---|---|---|
| **Weight, kg** | +2.4 (7.9) | +1.6 (7.8) |
| **BMI, kg/m²** | +0.95 (3.0) | +0.6 (2.9) |
| **Waist circumference, cr** | +1.5 (7.6) | +0.6 (6.9) |

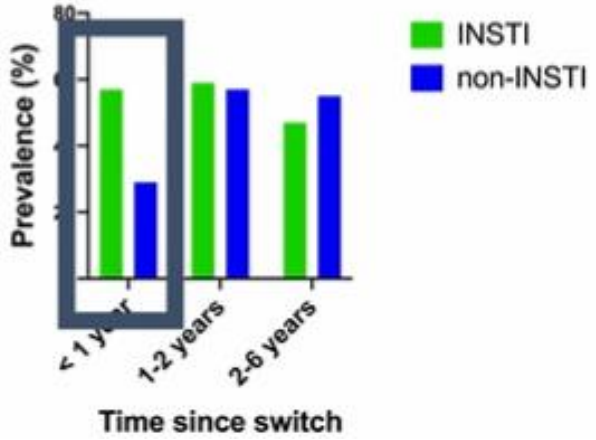
## Differences in measures of Hepatic Steatosis, Fibrosis, and FAST Scores between INSTI & Non-INSTI

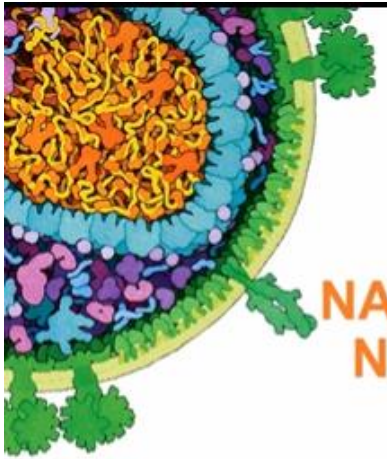





- Women on INSTIs had a **3.6 greater odds of having hepatic steatosis** within 1 year of switch compared to non-INSTI Controls.
- **No differences between groups in odds of moderate fibrosis** at any time-point.





THEMED DISCUSSION: TD-02

Monday, February 20, 2023

# NAFLD AND ITS COMBINATION WITH NASH PREDICT DM DEVELOPMENT IN PEOPLE WITH HIV

**Win Min Han**

*Thai Red Cross AIDS Research Center, Bangkok, Thailand*

Disclosure(s): No financial relationships to disclose.

30th CROI 2023

## Study design

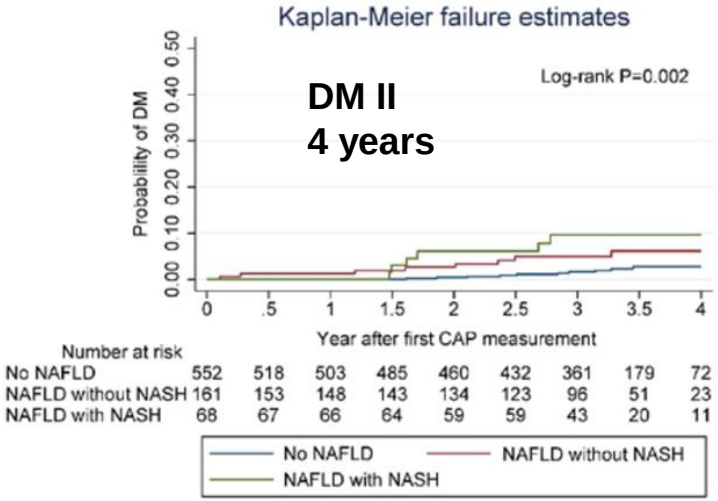
- A prospective cohort study
- Location – Bangkok, Thailand
- **NAFLD** – defined as CAP >248 dB/m (Karlas T, J Hepatol 2017)
- **NASH with significant activity and liver fibrosis** – defined as FibroScan-AST (FAST) score* ≥0.67

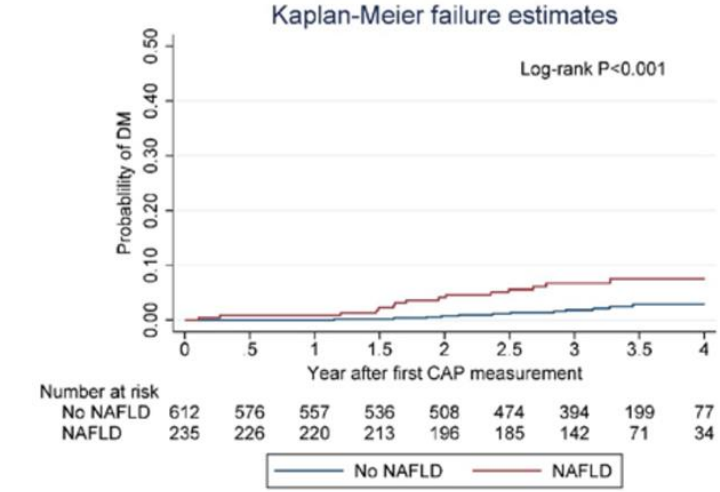
## Study population

- PWH aged ≥18 years without hepatitis B or C virus infection and without excessive alcohol consumption AND without DM diagnosis prior to baseline
- Baseline was defined as the first FibroScan date

## Study population

- 847 PWH included; median age at baseline was 46 (IQR 39-52) years (43% female)
- 90% had HIV RNA ≤50 copies/mL; w/ median CD4 - 588 (433-579) cells/mm$^3$
- Duration of ART: 11 (6-18) years; median CAP measurement: 3 (3-4)
- At baseline, 66% NNRTI, 20% PI, 9% INSTI and 6% others (6% TAF)
- 28% and 15% had NAFLD and NASH at baseline; 28 developed DM




## Summary

- Among well-suppressed PWH in a Thai cohort, **NAFLD alone** or **combined with NASH w/ liver fibrosis** predicts **new-onset DM**
- Secondary analyses – show the association of **DM with NAFLD at baseline** and **TAF use** (time-updated) with **incident NASH** by FAST score
- These results highlight the need for DM and CVD risks assessments and management in PWH with NAFLD
- Further mechanistic studies investigating underlying metabolic associations of NAFLD or NASH and DM development in PWH are warranted

# NAFLD / NASH / Liver fibrosis

**1** Prevalence

- 50% steatosis
- Almost 10% fibrosis
- MAFLD ♀18% / ♂24%

**2** Risk factors

- Metabolic risk factors
- INSTI (2000HIV cohort and WISH cohort)
- d4T

**3** Sex

**Women:**

- Less MAFLD
- More fibrosis
- Women >50y

**4** Consequences

**New-onset DM** predictors

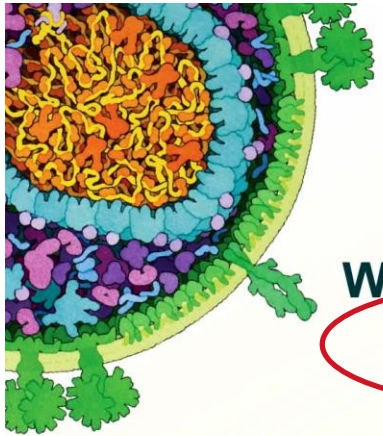
- NAFLD +/- NASH
- TAF

**5** Interventions

X

# 2.
# Metabolism
# Cardiovascular

## INSTIs Impact



THEMED DISCUSSION: TD-11

Wednesday, February 22, 2023

# WEIGHT GAIN AMONG PARTICIPANTS SWITCHING TO A DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA

**Kassem Bourgi**

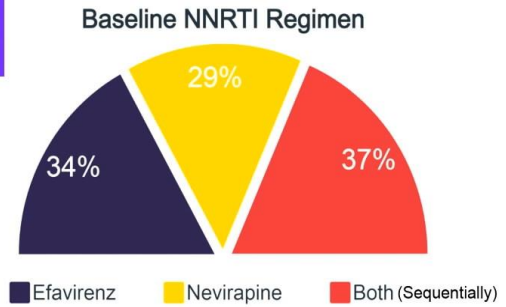
*Indiana University, Indianapolis, IN, United States*

30th CROI 2023

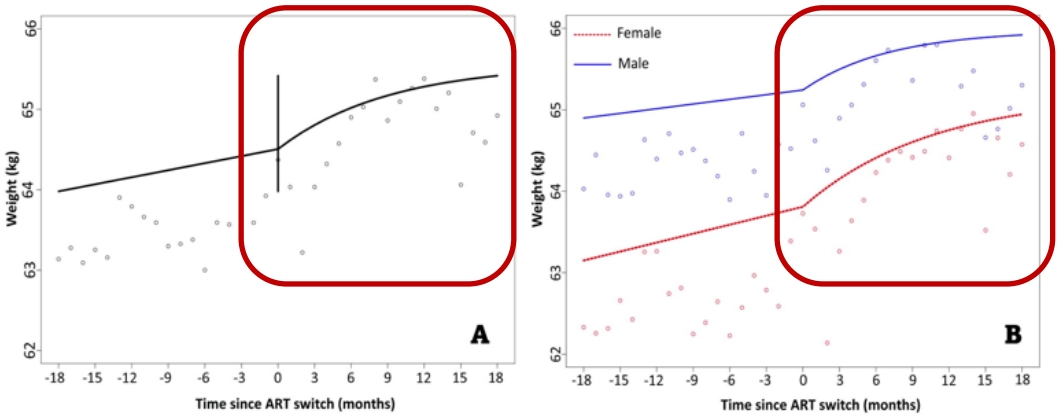
# Study Population

| N | Gender | Baseline Age |
|---|---|---|
| 23,131 subjects | **52% Female**<br>**48% Male** | 50 years<br>IQR (44 , 57) |

| Baseline BMI | BMI category |
|---|---|
| 22 $kg/m^2$<br>IQR (20, 25) | 12% underweight<br>28% overweight or obese |

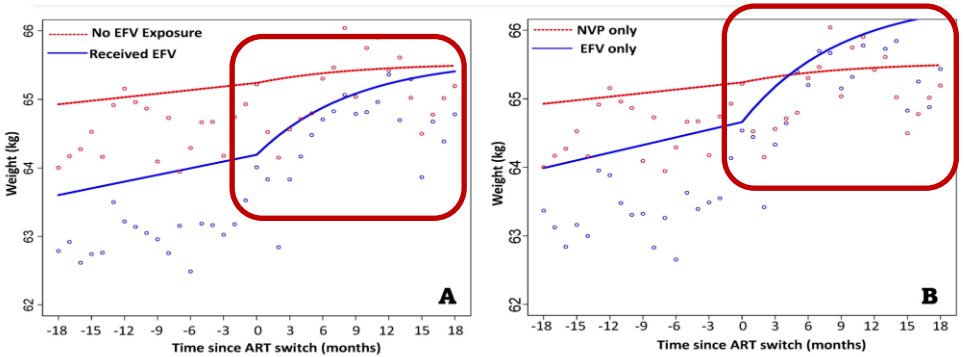


## Changes in the rate of weight gain after ART switch for overall participants (A), and by gender (B).




18 Months

## Changes in Rate of Weight Gain After Switch by baseline NNRTI drug




(A): EFV group includes participants exposed to both EFV and NVP
(B): EFV group includes participants exposed to EFV only

# Conclusions

Overall, the rate of weight gain increased, albeit modestly, after switching from an NNRTI to a DTG-based regimen.

The rate of weight gain was significantly higher for females compared to males following DTG switch.

Participants switching from EFV exhibited a significant increase in rate of weight gain following DTG switch while those switching from NVP had no changes in the rate of weight gain.

- Is the increase in the rate of weight gain observed a reflection of the **obesogenic effects of DTG** or a result of the withdrawal of the **anorectic effects of EFV**?
- Does the INSTI-associated "increased weight gain" phenomenon have more to do the comparator groups than with INSTIs?

# Changes in Body Mass Index with Longer-Term Integrase Inhibitor Use in REPRIEVE

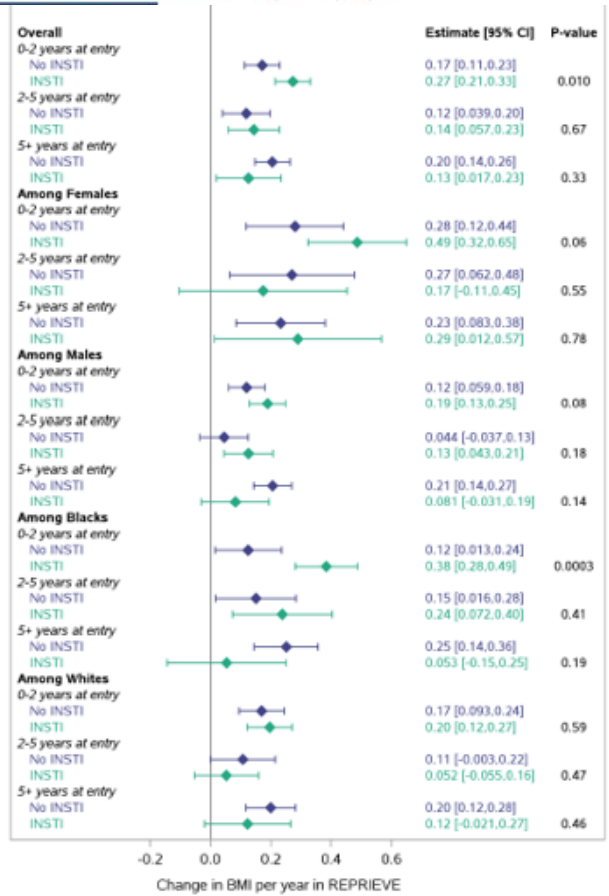
706

**Emma M Kileel**[1], Carlos D Malvestutto[2], Janet Lo [1], Kathleen V Fitch[1], Carl J Fichtenbaum[3], Judith A Aberg[4], Markella V Zanni[1], Esteban Martinez[5], Nwora Lance Okeke[6], Princy Kumar[7], Esau Joao[8], Sara McCallum[1], Pamela S Douglas[6], Heather J Ribaudo[9], Steven K Grinspoon[1], **for REPRIEVE investigators**

[1]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [2]Ohio State University Medical Center, Columbus, OH, USA, [3]University of Cincinnati College of Medicine, Cincinnati, USA, [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [5]Hospital Clinic and University of Barcelona, Barcelona, Spain, [6]Duke University School of Medicine, Durham, NC, USA, [7]Georgetown University School of Medicine, Washington, District of Columbia, USA, [8]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, [9]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, U.S.A.

## RESULTS

- 5475 REPRIEVE participants, including 2493 INSTI users were included.
- Increases in BMI associated with INSTI use over the follow-up period were greatest among those on their entry ART regimen for 2 years or less, females, and Black/African American participants. And baseline weight
- For those on their entry ART regimen for more than 2 years, significant weight gain related to INSTI use was not seen over the follow-up period.
- Results were generally similar accounting for differences in TDF and TAF use.



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

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

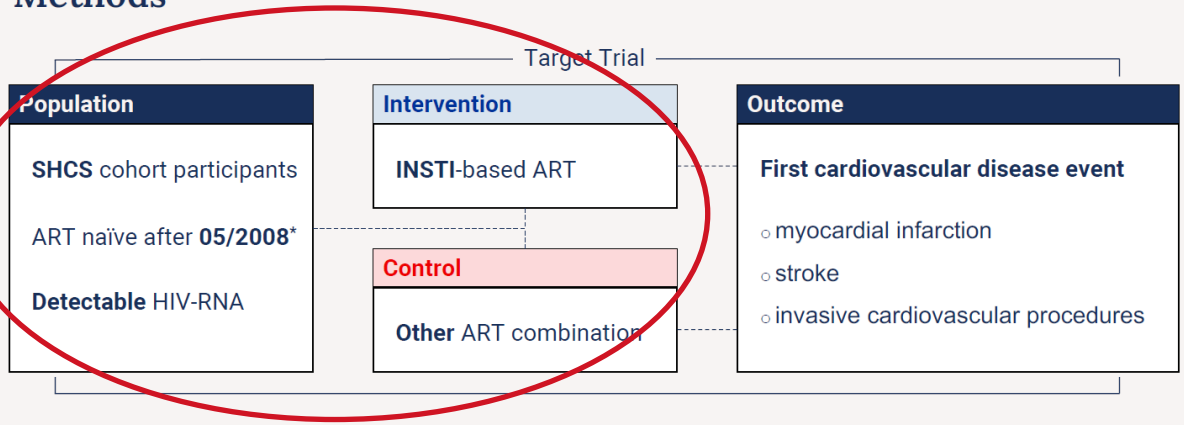
*Department of Infectious Diseases, Inselspital Bern University Hospital, Switzerland*

SWISS HIV COHORT STUDY

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

*Financial Disclosures:*
*The institution of BS has received travel grants from Gilead Sciences and ViiV Healthcare.*

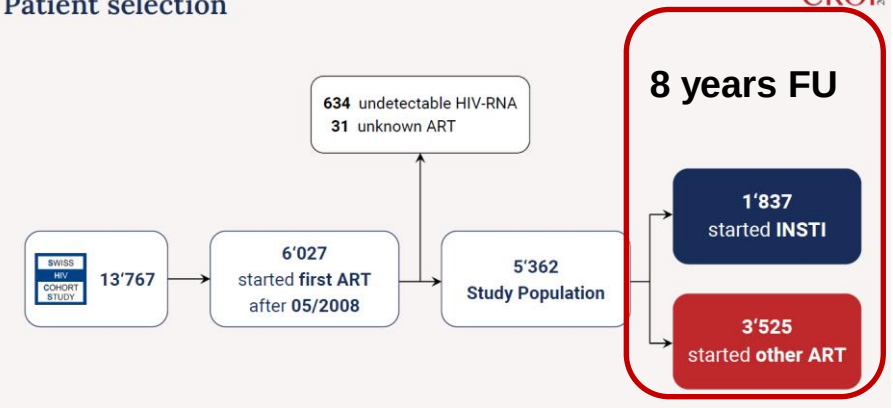
## Methods




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

**Evaluate the impact of starting INSTI-based ART on cardiovascular disease events in treatment-naïve PLWH**

## Patient selection

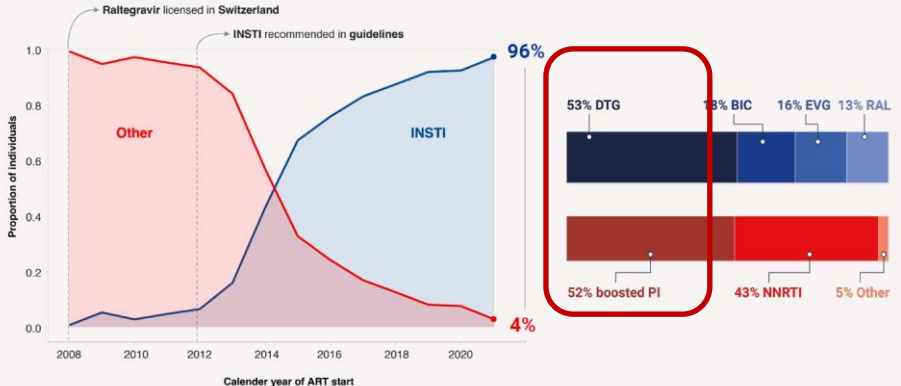


## Patient characteristics

| | INSTI | Other ART |
|---|---|---|
| Age | 39 years (31 to 50) | 38 years (31 to 46) |
| Body mass index | 24 kg/m² (21 to 26) | 23 kg/m² (21 to 26) |
| Nadir CD4 cell count | 330/µL (188 to 482) | 278/µL (171 to 372) |
| Women | 16% | 24% |
| African Origin | 11% | 18% |
| History of CVD | 1.5% | 1.5% |
| Current smoking | 46% | 47% |
| Arterial Hypertension | 10% | 10% |
| Lipid lowering Treatment | 2.6% | 1.8% |
| Diabetes | 2.1% | 1.8% |
| Abacavir | 23% | 12% |
| Tenofovir alafenamide | 40% | 1.4% |

Surial B

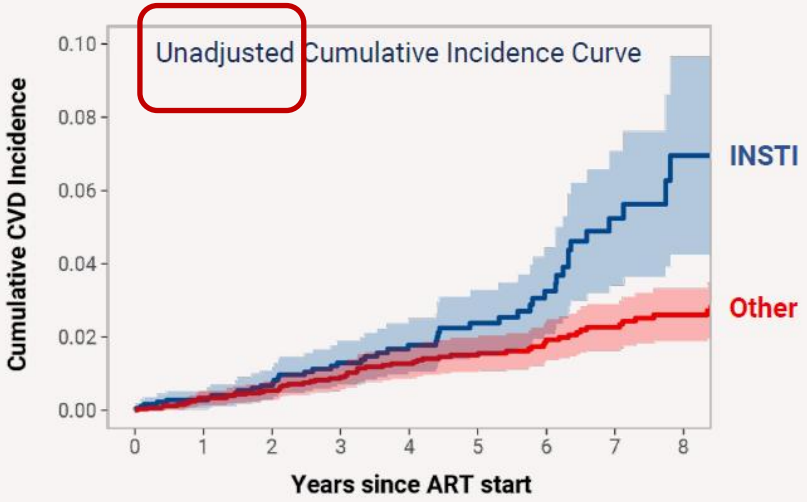
## Use of INSTI as initial ART in the SHCS



# Cardiovascular disease events

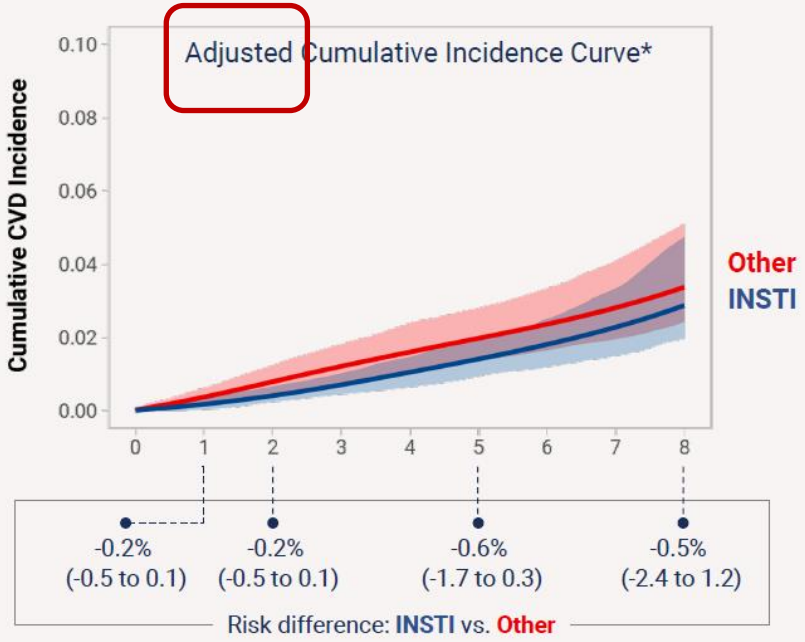
30th CROI 2023

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




**Number at risk**

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




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

Surial B

# Weight and Metabolic Changes With Cabotegravir + Rilpivirine Long-Acting or Bictegravir/Emtricitabine/Tenofovir Alafenamide

Darrell H. S. Tan[1], Andrea Antinori[2], Beng Eu[3], María José Galindo Puerto[4], Clifford Kinder[5], Donna Sweet[6], Cornelius N. Van Dam[7], Kenneth Sutton[8], Denise Sutherland-Phillips[8], Alessandro Berni[9], Feifan Zhang[10], William R. Spreen[8], Harmony P. Garges[8], Parul Patel[8], Ronald D'Amico[8]

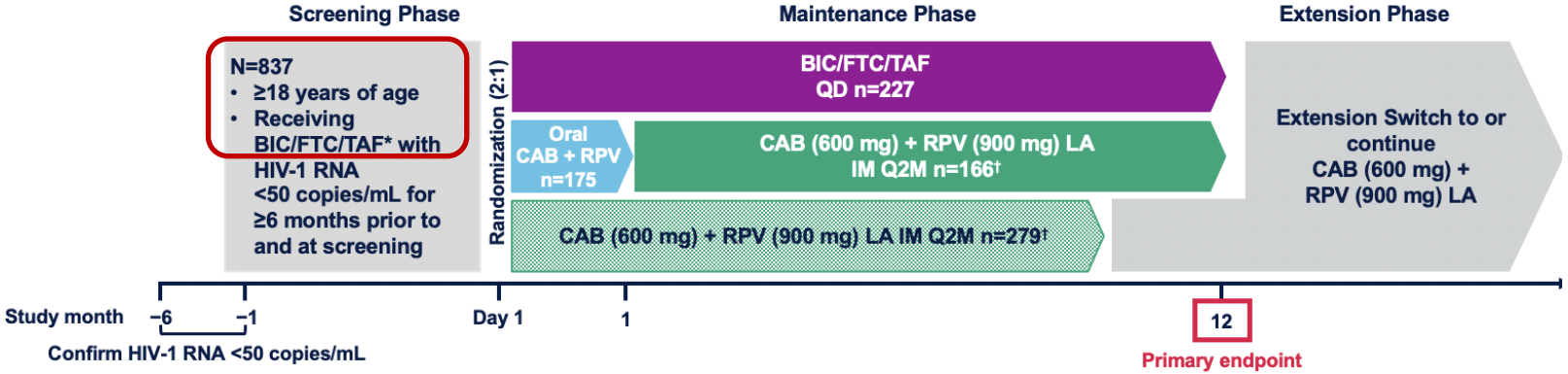
*[1]Division of Infectious Diseases, Department of Medicine, St Michael's Hospital, Toronto, ON, Canada; [2]HIV/AIDS Department, National Institute for Infectious Diseases, "Lazzaro Spallanzani" IRCCS, Rome, Italy; [3]Prahran Market Clinic, Prahran, Victoria, Australia; [4]Universitat de València, Valencia, Spain; [5]AIDS Healthcare Foundation–The Kinder Medical Group, Miami, FL, United States; [6]University of Kansas School of Medicine-Wichita, KS, United States; [7]Regional Center for Infectious Diseases, Cone Health, Greensboro, NC, United States; [8]ViiV Healthcare, Durham, NC, United States; [9]GSK, Brentford, United Kingdom; [10]GSK, Collegeville, PA, United States*

Darrell Tan, MD, PhD, reports salary support from the Canada Research Chairs Program, investigator-initiated research grants to his institution from Abbott and Gilead Sciences, Inc., and support to his institution for clinical trials sponsored by GSK

**SOLAR Study**

# SOLAR Study Design and Metabolic Objectives

**Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study**




- Metabolic Objectives: Changes in body weight, body mass index (BMI) category, waist and hip circumferences, waist-to-height ratio, waist-to-hip ratio,‡ and the proportion of participants with insulin resistance or metabolic syndrome§ were assessed from baseline (Day 1) to Month 11 (SWI)/12 (OLI) (hereafter referred to as Month 12)

*A single prior integrase inhibitor regimen is allowed if BIC/FTC/TAF is a second-line regimen 6 months prior to screening. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must not have been done for treatment failure (HIV-1 RNA ≥400 copies/mL). †Participants randomized to the LA arm were offered an optional OLI; the decision to dose SWI or with OLI was determined by the participants following informed consent discussions with the investigator. ‡Standardized weight and anthropometric measurements were performed using circumference tapes and Tanita scales. §As defined by standard clinical criteria.

# Baseline Characteristics

| Parameter | CAB + RPV LA Q2M arm (n=454) | BIC/FTC/TAF (n=227) |
|---|---|---|
| Age (years), median (range) | 37 (18–74) | 37 (18–69) |
| ≥50 years, n (%) | 89 (20) | 45 (20) |
| Female (sex at birth), n (%) | 79 (17) | 41 (18) |
| Race, n (%) | | |
| Black | 96 (21) | 49 (22) |
| White | 313 (69) | 160 (70) |
| Asian | 23 (5) | 11 (5) |
| Other races* | 22 (5) | 7 (3) |
| BMI (kg/m$^2$), median (IQR) | 26.0 (23.2–29.3) | 25.4 (23.6–29.6) |
| ≥30 kg/m$^2$ | 97 (21) | 52 (23) |
| Weight (kg), median (IQR) | 81.3 (70.7–91.8) | 79.0 (69.4–91.7) |
| CD4+ cell count (cells/mm$^3$), median (IQR) | 662 (487–853) | 645 (489–823) |
| Duration of prior ART (years), median (IQR)† | 2.6 (1.6–4.9) | 2.5 (1.5–4.7) |

- Among study participants, 12 transgender females, 1 transgender male, and 1 gender non-conforming individual were included

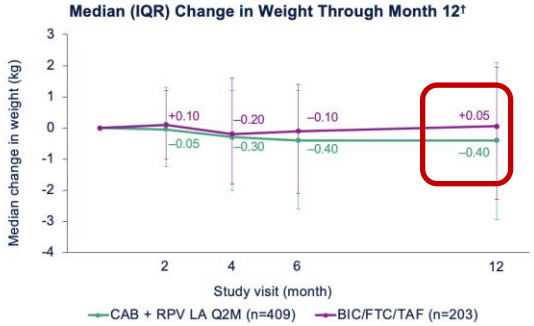
*Other race participants: American Indian or Alaska Native, n=14 (CAB + RPV LA Q2M) and n=2 (BIC/FTC/TAF); Native Hawaiian or other Pacific Islander, n=1 (BIC/FTC/TAF); multiple, n=8 (CAB + RPV LA Q2M) and n=4 (BIC/FTC/TAF).
†BIC/FTC/TAF must have been the participant's first or second regimen. If BIC/FTC/TAF was the second regimen, the first regimen must have been an integrase inhibitor.

# Pertinent Baseline Metabolic Parameters, Medical History, and Co-medications History

| Parameter | CAB + RPV LA Q2M arm (n=454) | BIC/FTC/TAF (n=227) |
|---|---|---|
| BMI category, n (%) | | |
| Underweight (<18.5 kg/m$^2$) | 8 (2) | 3 (1) |
| Normal (18.5–<25 kg/m$^2$) | 175 (39) | 94 (41) |
| Overweight (25–<30 kg/m$^2$) | 174 (38) | 78 (34) |
| Obesity (≥30 kg/m$^2$) | 97 (21) | 52 (23) |
| Baseline lipids, median (range) | | |
| TG (mmol/L) | 1.07 (0.32–20.42) | 1.06 (0.38–4.01) |
| TC (mmol/L) | 4.58 (2.25–9.66) | 4.77 (2.72–8.94) |
| LDL (mmol/L) | 2.74 (0.55–5.41) | 2.77 (1.01–6.97) |
| HDL (mmol/L) | 1.22 (0.47–2.38) | 1.26 (0.60–3.06) |
| TC/HDL ratio | 3.71 (1.45–20.55) | 3.56 (1.82–8.25) |
| Relevant medical history, n (%) | | |
| Hypertension | 48 (11) | 26 (12) |
| Diabetes | 19 (4) | 7 (3) |
| Relevant co-medications, n (%) | | |
| Lipid-lowering therapy* | 40 (9) | 21 (9) |

- In total, 59% (n=401/681) of participants were in the overweight or obesity category at baseline

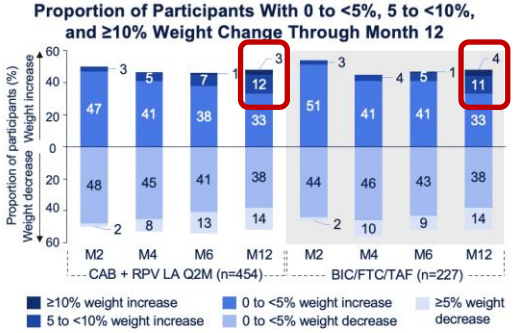
## Change in Weight Through Month 12 by Treatment Regimen*




- At Month 12, median (IQR) change in weight in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg and +0.05 (-2.30, +1.95) kg in the BIC/FTC/TAF group

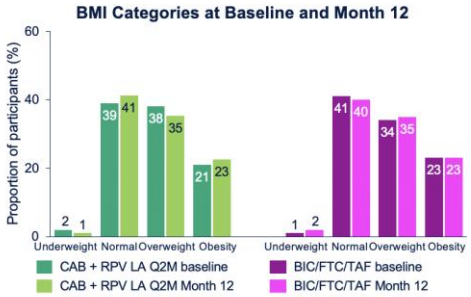
*Any participant that started lipid-modifying agents during the study was non-evaluable in anthropometric assessments. †Median (IQR) weight (kg) at baseline: CAB + RPV LA, 81.3 (70.70, 91.80); BIC/FTC/TAF, 79.0 (69.40, 91.70).

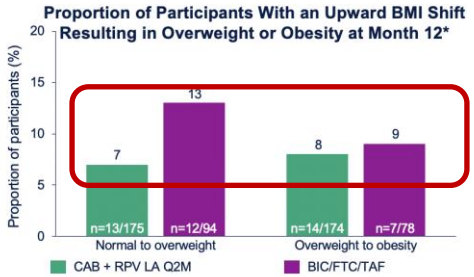
## Percent Change in Weight Through Month 12 by Treatment Regimen*




- Weight increase of ≥10% by Month 12 occurred in 3% (n=11/454) of participants in the LA arm vs. 4% (n=9/227) in the BIC/FTC/TAF arm

## Change in BMI Through Month 12 by Treatment Regimen

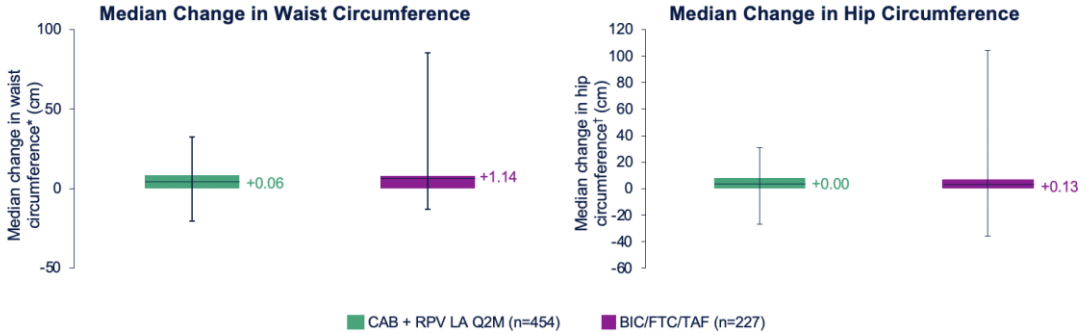



- Overall, the proportion of individuals in BMI categories remained similar at Month 12

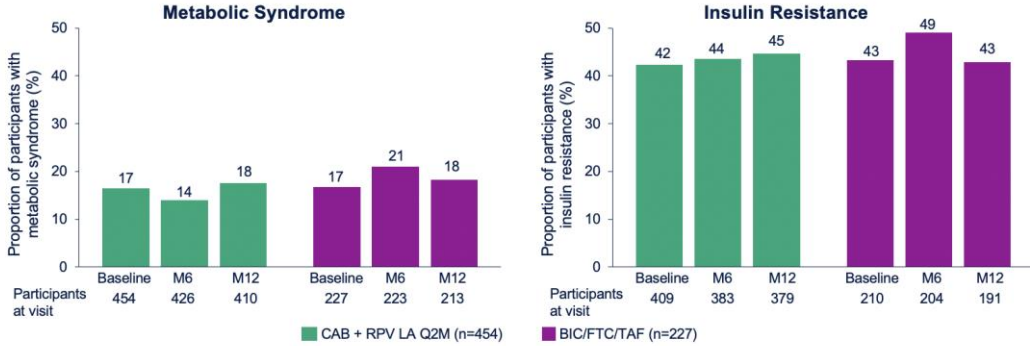
*No participant shifted from normal to obesity or underweight to overweight.

# Change in Waist Circumference and Hip Circumference Through Month 12 by Treatment Regimen




- There were no clinically relevant changes from baseline to Month 12 in the median WHtR‡ (CAB + RPV LA Q2M, +0.000; BIC/FTC/TAF, +0.010) and median WHR§ (CAB + RPV LA Q2M, +0.000; BIC/FTC/TAF, +0.010)

# Metabolic Syndrome* and Insulin Resistance† Through Month 12 by Treatment Regimen




- There were no clinically relevant changes from baseline to Month 12 in the proportion of participants with metabolic syndrome or insulin resistance in either arm

# 2.
# Metabolism
# Cardiovascular

## Interventions (Reversibility?)

# WEIGHT LOSS AND METABOLIC CHANGES AFTER SWITCHING FROM TAF/FTC+DTG TO TDF/3TC/DTG

CROI 671
February 19-22nd 2023, Seattle USA

**Bronwyn Bosch**[1], Godspower Akpomiemie[1], Nomathemba Chandiwana[1], Simiso Sokhela[1], Andrew Hill[2], Kaitlyn McCann[3], Ambar Qavi[3], Manya Mirchandani[3], Francois Venter[1]
[1]Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2]Department of Pharmacology and Therapeutics, University of Liverpool, United Kingdom. [3]Faculty of Medicine, Imperial College, London, UK

ADVANCED Study → CHARACTERISE Study

## METHODS

- In the ADVANCE trial, 1053 treatment naïve participants in South Africa were randomized to TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV for 192 weeks.
- After Week 192, participants were switched to open-label TDF/3TC/DTG for at least 52 weeks in a follow up trial, CHARACTERISE.
- At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA.
- Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TDF/3TC/DTG were evaluated in each treatment arm using paired non-parametric tests.

**52 Wks FU**

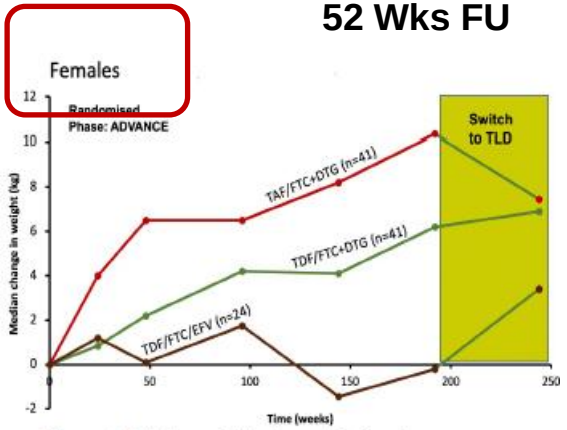



**Figure 1**: Median weight change for females

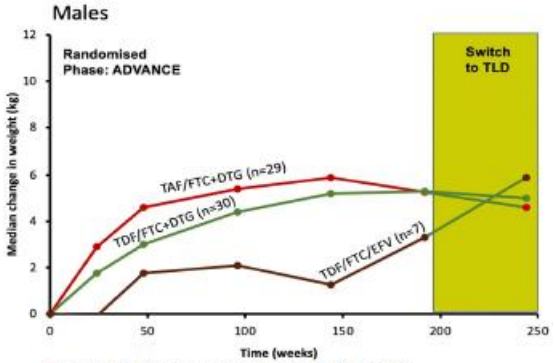



**Figure 2:** Median weight change for males

**Table 1**: Baseline characteristics and changes in weight and metabolic parameters from switch to TDF/3TC+DTG by original treatment received. *Note: Continuous variables are displayed as Median and interquartile range (IQR). Count variables are displayed as n/N and %. n.s. = not significant

| Group | TAF/FTC+DTG (n=70) | TDF/FTC+DTG (n=71) | TDF/FTC/EFV (n=31) |
|---|---|---|---|
| **Baseline characteristics*** | | | |
| Sex (% Female) | 41/70 (59%) | 41/71 (58%) | 24/31 (77%) |
| Country (% South Africa) | 42/70 (60%) | 51/71 (72%) | 20/31 (64%) |
| Weight (kg) | 81.1 [71.5, 89.1] | 72.9 [61.7, 86.3] | 74.3 [61.8, 100.5] |
| BMI (kg/m$^2$) | 28.0 [23.9, 31.8] | 25.9 [22.5, 30.6] | 25.6 [23.6, 33.1] |
| HIV RNA <50 copies/mL (%) | 66/67 (98%) | 62/64 (97%) | 23/23 (100%) |
| CD4 count (cells/uL) | 560 [424, 787] | 549 [407.5, 743.5] | 677 [544, 882] |
| Cholesterol (mmol/L) | 3.9 [3.5, 4.8] | 3.7 [3.2, 4.3] | 4.5 [3.6, 4.91] |
| LDL (mmol/L) | 2.6 [2.2, 3.1] | 2.3 [1.9, 2.9] | 2.8 [2.3, 3.27] |
| HDL (mmol/L) | 1.1 [0.9, 1.3] | 1.1 [0.9, 1.3] | 1.3 [1.0, 1.6] |
| Triglycerides (mmol/L) | 0.9 [0.7, 1.2] | 0.8 [0.6, 1.0] | 0.9 [0.7, 1.3] |
| Fasting glucose (mmol/L) | 4.9 [4.5, 5.2] | 4.9 [4.6, 5.1] | 4.7 [4.5, 5.1] |
| HbA1c (mmol/L) | 5.5 [5.1, 5.7] | 5.5 [5.2, 5.7] | 5.5 [5.2, 5.7] |
| Systolic blood pressure (mmHg) | 127 [119, 134] | 122 [117, 132] | 118 [113, 126] |
| Diastolic blood pressure (mmHg) | 83 [78, 88] | 82 [77.5, 86] | 76 [72, 83] |
| **Changes from switch*** | | | |
| Weight (kg) | -1.2 [-3.8,1], p=0.006 | -0.1 [-2.1, 2.2] (n.s.) | +2.9 [-0.7, 4.9], p=0.02 |
| BMI (kg/m$^2$) | -0.4 [-1.3, 0.3], p=0.005 | -0.05 [-0.7, 0.7] (n.s.) | +1.0 [-0.2, 1.9], p=0.022 |
| Total cholesterol (mmol/L) | -0.2 [-0.5, 0.1], p=0.002 | +0.2 [-0.1, 0.4], p=0.001 | -0.3 [-0.8, 0.01], p=0.011 |
| LDL cholesterol (mmol/L) | -0.3 [-0.6, -0.01], p<0.001 | -0.01 [-0.2, 0.2] (n.s.) | -0.3 [-0.5, -0.1], p=0.001 |
| HDL (mmol/L) | -0.03 [-0.2, 0.1] (n.s.) | +0.04 [-0.1, 0.2], p=0.021 | -0.1 [-0.3, 0.05], p=0.049 |
| Triglycerides (mmol/L) | -0.1 [-0.3, 0.09], p=0.025 | -0.02 [-0.2, 0.2] (n.s.) | -0.1 [-0.3, 0.05], p=0.057 |
| Fasting glucose (mmol/L) | -0.2 [-0.5, 0.1], p<0.001 | 0 [-0.3, 0.2] (n.s.) | -0.1 [-0.3, 0.1] (n.s.) |
| HbA1c (mmol/L) | -0.1 [-0.3, 0], p<0.001 | -0.1 [-0.3, 0.1] (n.s.) | -0.15 [-0.2, 0], p=0.008 |
| Systolic blood pressure (mmHg) | +1.5 [-6, 14] (n.s.) | +3 [-2.5, 10], p=0.021 | +6 [-10, 13] (n.s.) |
| Diastolic blood pressure (mmHg) | +2 [-4, 6] (n.s.) | +0.5 [-5.5, 4.5] (n.s.) | +2 [-4, 11] (n.s.) |
| HIV RNA<50 copies/mL at or after week 52 (%) | 68/68 (100%) | 68/70 (97%) | 25/28 (89%) |

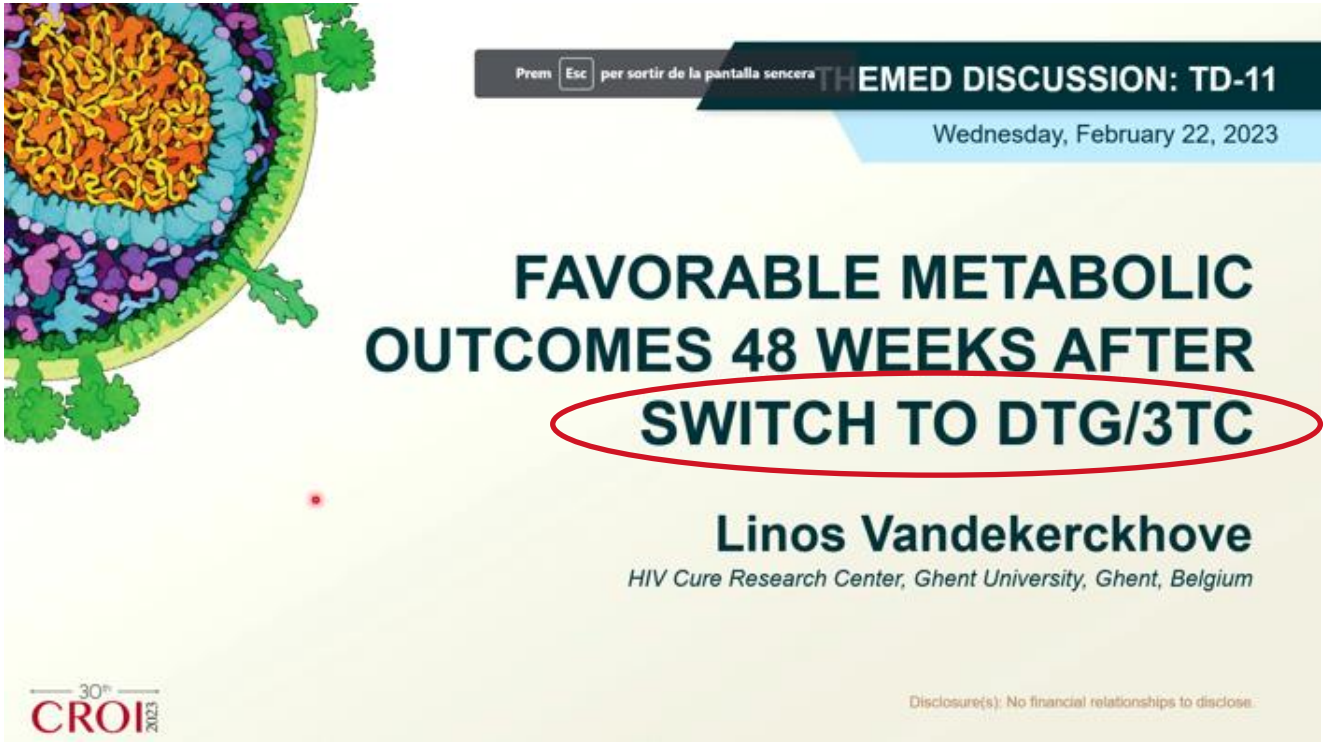
After switching from TAF/FTC+DTG to TDF/3TC/DTG for 52 weeks, there were statistically significant reductions in weight, total cholesterol, LDL, triglycerides, fasting glucose and HBA1C (Table 1).

Participants switching from TDF/FTC/EFV to TDF/3TC/DTG showed significant rises in body weight, with reductions in total cholesterol, LDL, HDL, triglycerides and HbA1C (Table 1).

WHO guidelines recommend TDF/3TC/DTG as first line treatment, with TAF only to be used for those with osteoporosis or renal impairment. The results from CHARACTERISE support the WHO guidelines.

## CONCLUSIONS

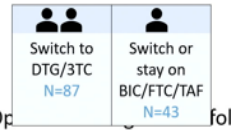
- After 4 years of weight gain on first-line TAF/FTC+DTG, switching to TDF/3TC/DTG for 52 weeks led to significant weight loss for women (median: -1.6kg, p=0.0125). This change in weight was not significant in men (median: -0.2kg, p=0.2561).
- There were concurrent reductions in total cholesterol, LDL, triglycerides, fasting glucose and HBA1C after switching TAF/FTC+DTG to TDF/3TC/DTG.


Prem Esc per sortir de la pantalla sencera
THEMED DISCUSSION: TD-11
Wednesday, February 22, 2023
FAVORABLE METABOLIC OUTCOMES 48 WEEKS AFTER SWITCH TO DTG/3TC
Linos Vandekerckhove
HIV Cure Research Center, Ghent University, Ghent, Belgium
30th CROI 2023
Disclosure(s): No financial relationships to disclose

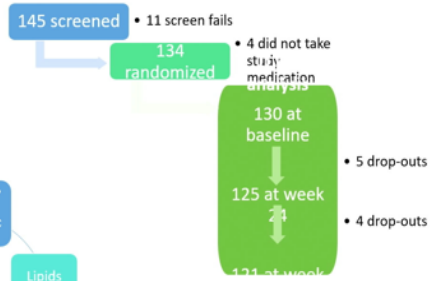
RUMBA Study

## Rumba study

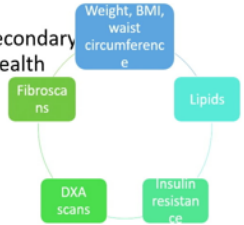
- Randomized controlled trial (2:1)




- Op follow-up




- Outcomes: focus on secondary endpoint: metabolic health




- Linear mixed models with covariance patterns

| Baseline characteristics | DTG/3TC (n = 87) | BIC/FTC/TAF (n = 43) | p-value |
|---|---|---|---|
| **Male sex** (%) | 90,8 | 90,7 | 1.000 |
| **Age** (mean ± SD) | 47,3 ± 11,9 | 45,0 ± 11,6 | 0.292 |
| **Non-European ethnicity** (%) | 19,5 | 25,6 | 0.628 |
| **Sexual orientation** (%) | | | 0.526 |
| Gay/lesbian or bisexual/pansexual | 70,1 | 67,4 | |
| Heterosexual | 27,6 | 30,2 | |
| **ART regimen at baseline** (%) | | | 0.072 |
| DTG/ABC/3TC | 31 | 51 | |
| BIC/FTC/TAF | 68 | 49 | |
| **Years on ART** (median (IQR)) | 8 (5-11) | 6 (4-9) | 0.133 |
| **Years on 2nd generation INSTI** (median (IQR)) | 3 (2-5) | 4 (3-5) | 0.476 |
| **CD4 nadir** (cells/µl; median (IQR)) | 206 (193-476) | 269 (212-380) | 0.510 |
| **Weight** (kg; mean ± SD) | 81 ± 12 | 75 ± 13 | 0.013 |
| **Waist** (cm; mean ± SD) | 95 ± 12 | 89 ± 11 | 0.006 |
| **BMI** (kg/m²; median (IQR)) | 26 (23-28) | 25 (22-26) | 0.024 |

# Results

1. Significant changes between treatment groups from baseline to week 48 (linear mixed models, adjusted for baseline BMI)

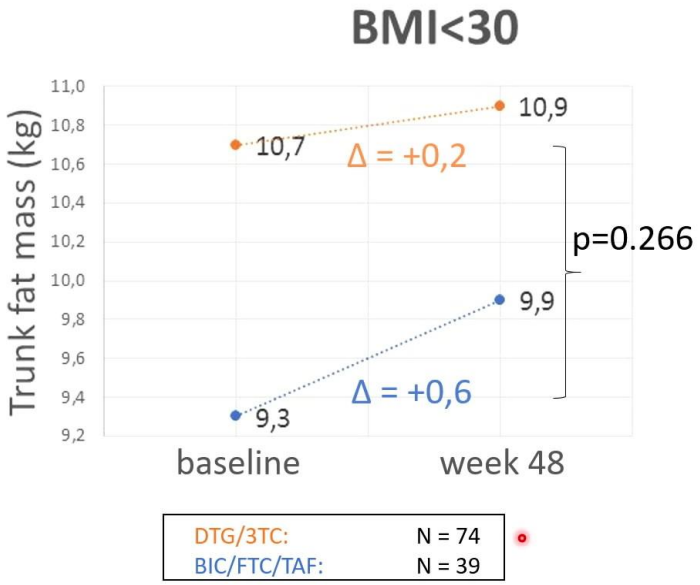
| | DTG/3TC | BIC/FTC/TAF | p-value |
|---|---|---|---|
| **ALT (U/L)** | - 0.73 | + 4.55 | 0.040 |
| **HDL (mg/L)** | - 0.043 | - 2.84 | 0.043 |
| **Lean trunk mass (gram)** | + 112 | - 474 | 0.032 |
| ***Trunk fat mass (gram)*** | + 41 | + 719 | 0.043 |
| **Fat percentage** | - 0.04 | + 1.32 | 0.003 |

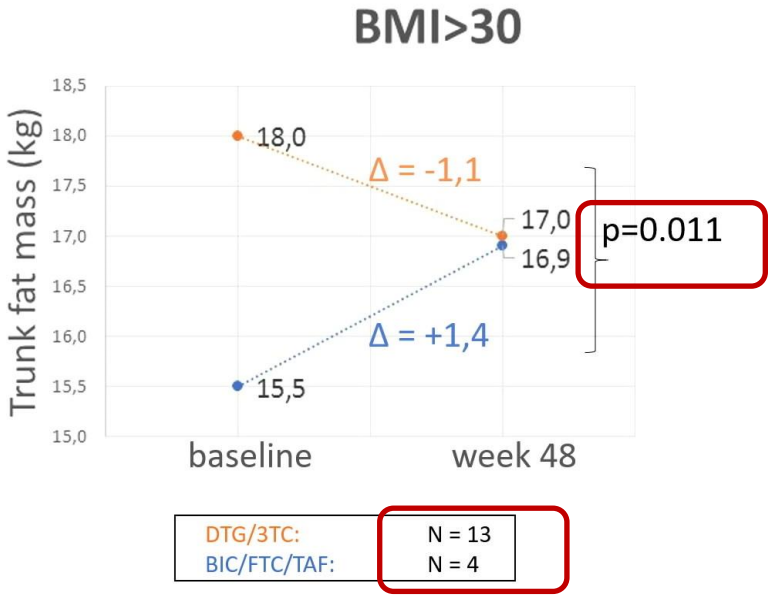
| | DTG/3TC | BIC/FTC/TAF | p-value |
|---|---|---|---|
| **Weight (kg)** | +0,29 | +0,30 | 0.987 |
| **Waist (cm)** | -0,07 | + 1,10 | 0.155 |
| **BMI (kg/m²)*** | +0,07 | +0,04 | 0.919 |
| **Cholesterol (mg/dl)** | -2,49 | -8,90 | 0.316 |
| **LDL cholesterol (mg/dl)** | -1,82 | -6,21 | 0.435 |
| **Triglycerides (mg/dl)** | -3,82 | -20,96 | 0.206 |
| **HOMA-IR** | -0,16 | -0,43 | 0.359 |
| **FibroCAP (dB/m)** | -0.39 | -11.61 | 0.304 |

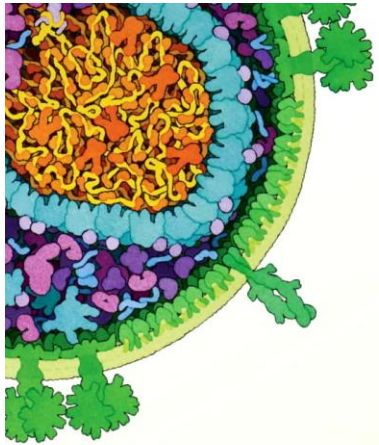
* Unadjusted for BMI baseline

# Results

2. Greater treatment-mediated differences in trunk fat in people with BMI > 30 (p=0.041)





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THEMED DISCUSSION: TD-11

Wednesday, February 22, 2023

# REVERSIBILITY OF TAF- AND/OR INSTI-ASSOCIATED WEIGHT GAIN


**Myrthe L. Verburgh**

*University of Amsterdam, Amsterdam, Netherlands*


30th CROI 2023

Disclosure(s): No financial relationships to disclose.

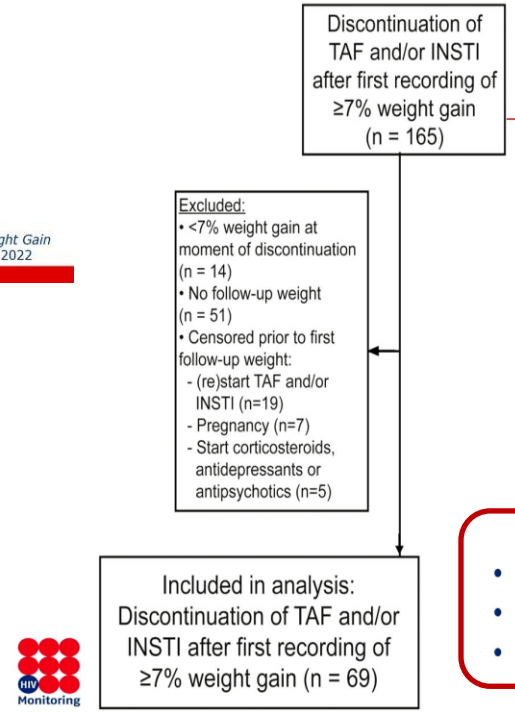
## Research question & Study population

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

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

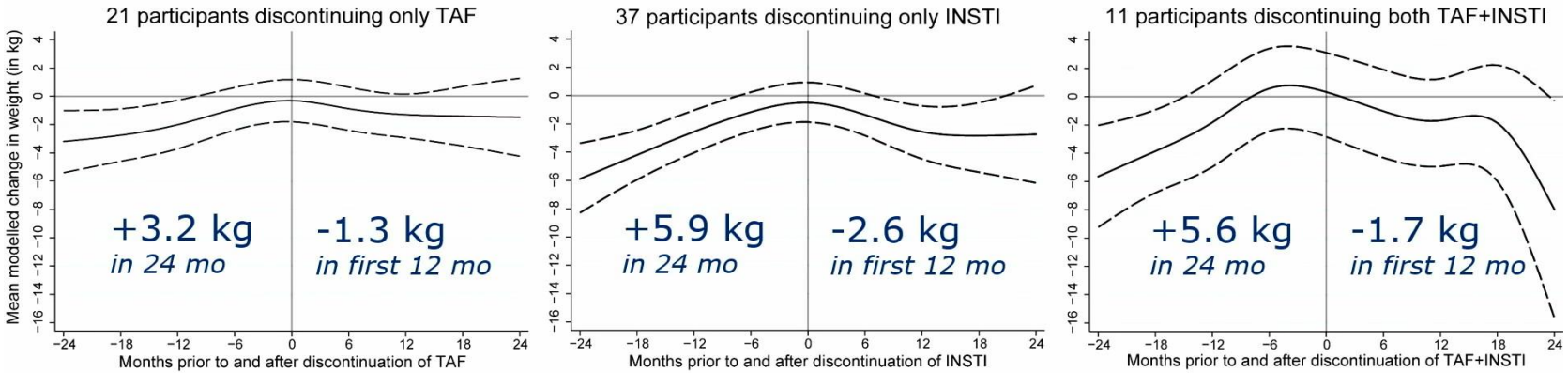
1. Verburgh et al. *One in 10 Virally Suppressed Persons With HIV in The Netherlands Experiences ≥10% Weight Gain After Switching to Tenofovir Alafenamide and/or Integrase Strand Transfer Inhibitor*. Open Forum Infect Dis. 2022

## Study population




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

# Adjusted mean modelled weight change prior/after discontinuation




## Factors associated with weight change after discontinuation

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

HIV Monitoring

# Conclusions & Discussion points

- TAF- and/or INSTI-associated weight gain of ≥7% appears to be only partly reversible after discontinuation
- No independent associations were found between weight change after discontinuation of TAF and/or INSTI and concomitant changes in NRTI backbone or anchor agent at moment of discontinuation
  - Only being obese was associated with greater reversibility of weight gain
- Limitation: limited sample size
- Is reversibility of weight gain the result of (re)starting weight-suppressive ARVs (like TDF or EFV) or the result of discontinuing weight gain-inducing TAF and/or INSTI?

HIV Monitoring

# Cardiovascular

## 1 INSTIs and Metabol

### Study from Kenya (NNRTI→ DTG)

- Modest increase in weight
- Higher in Women
- Higher in those from EFV

### REPRIEVE Study

- Modest increase in weight
- Higher in Women, Black people and baseline high weight, during 2 years

### CAB+RPV: SOLAR

- Similar Weight and Antropo. measurements to BIK

## 2 INSTIs and CV events

### Swiss cohort

- INSTIs similar to No-INSTIs (8y FU)

## 3 REVERSIBILITY?

### Characterise Study

- TAF/FTC+DTG → TDF/3TC/DTG decreased Weight and Metabolic in Women (52wks)

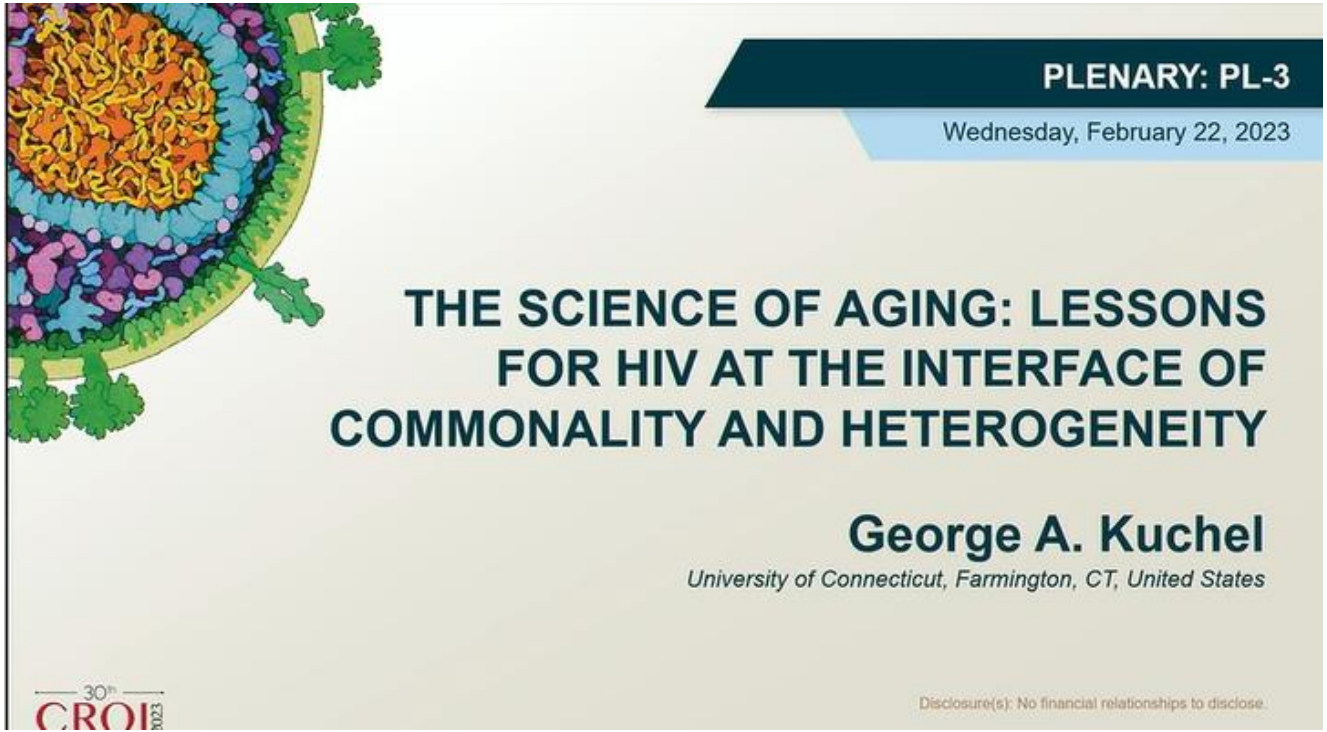
### Switch Study (Belgium)

- Higher decrease in fat mass with Dovato vs. BIK
- Higher if BMI≥30

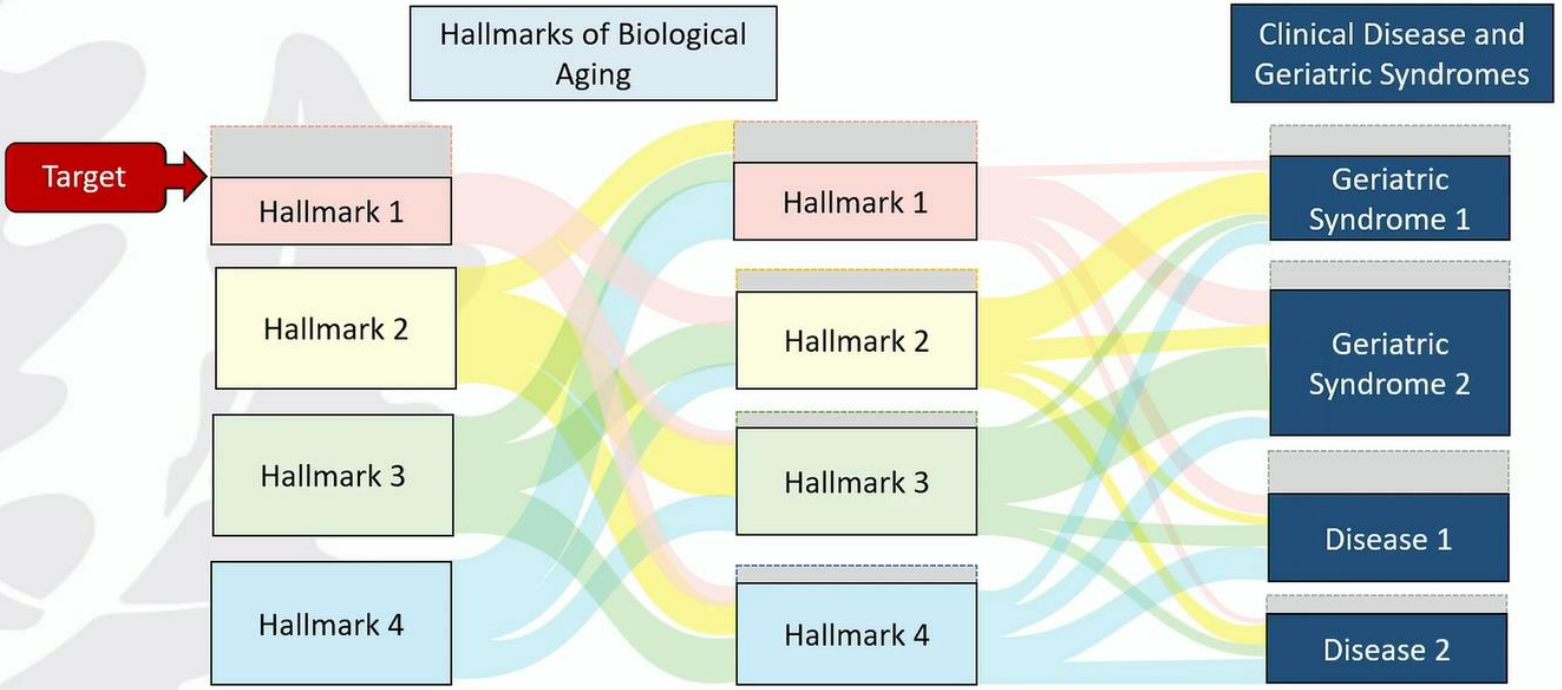
### Switch Study (Amsterdam)

- Higher decrease in Weight in those who stop TAF and/or INSTIs with >7% weight gain
- Higher if BMI≥30

# 4.
# Miscelanea


PLENARY: PL-3
Wednesday, February 22, 2023
THE SCIENCE OF AGING: LESSONS FOR HIV AT THE INTERFACE OF COMMONALITY AND HETEROGENEITY
George A. Kuchel
University of Connecticut, Farmington, CT, United States
30th CROI 2023
Disclosure(s): No financial relationships to disclose

# Unitary Theory of Fundamental Aging Mechanisms




*Espinoza, Justice, Newman, Pignolo and Kuchel; Chapter 40 Applied Clinical Geroscience, Hazzard's Geriatric Medicine and Gerontology, 8th edition*

UCONN CENTER ON AGING



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**Exercise, smoking cessation, healthy nutrition and a focus on patient-centered goals remain essential irrespective of HIV and Geroscience**

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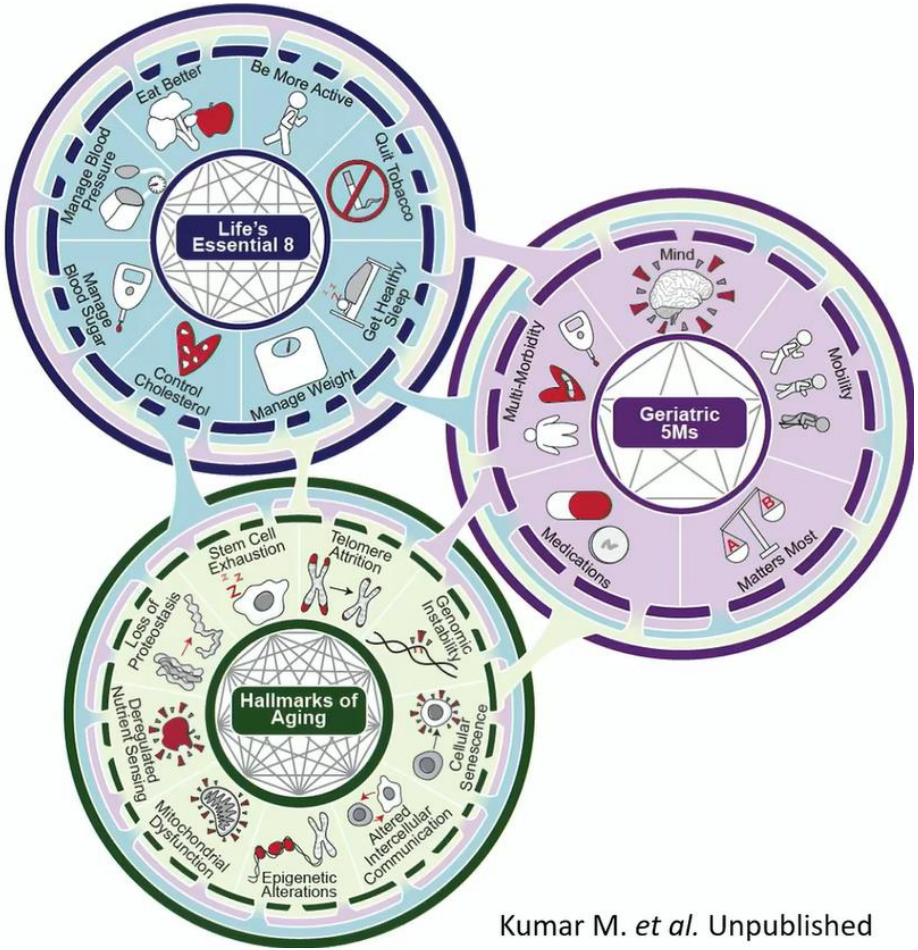
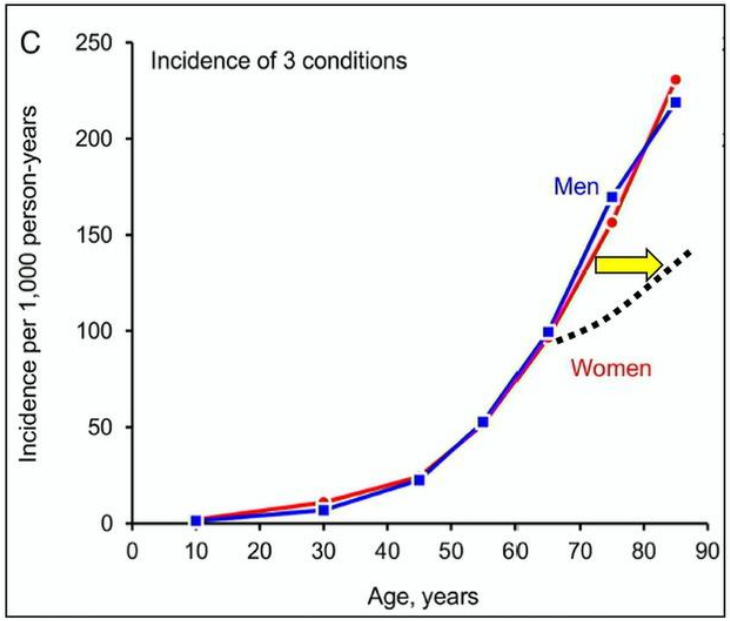


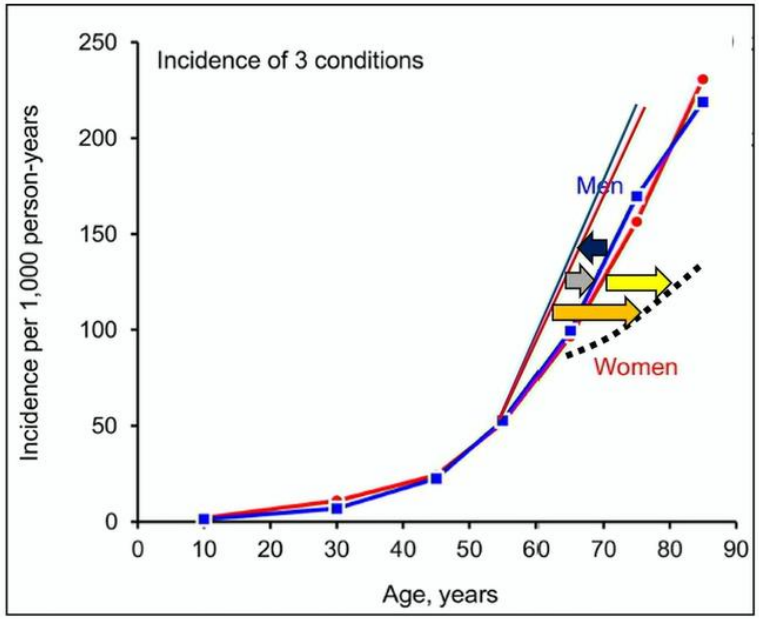

Kumar M. *et al.* Unpublished

# Reframing The Geroscience Hypothesis in the Context of HIV

## Without HIV




## With HIV

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Masters MC *et al*. J Acquir Immune Defic Syndr. 2022 89:S34-S46. PMID: 35015744.



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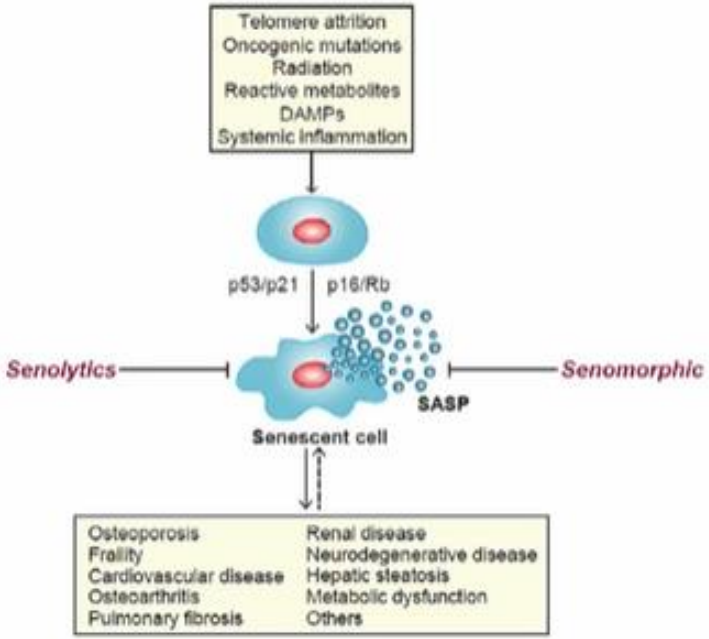
# Proposal for first geroscience-guided clinical trial in Older PWH




**<u>Dasatinib + Quercetin (D + Q)</u>:**

- "Repurposed" compounds function as senolytics
- Improve frailty and mobility in animal and pre-clinical human studies
- Excellent safety profiles when used in a "hit and run" manner
- NIA Translational Geroscience Network (R33 AG061456)

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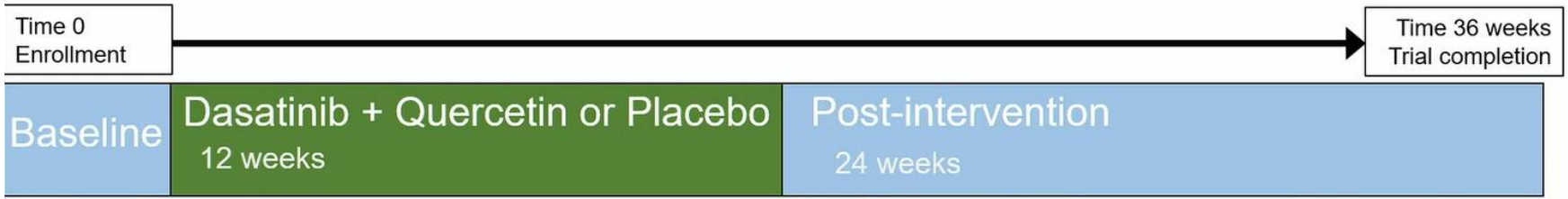
# Proposal for first geroscience-guided clinical trial in Older PWH




**Inclusion criteria**

- HIV-1 positive on ART for ≥ 2 years
- ≥ 50 years old
- HIV diagnosis ≥ 10 years prior to study entry
- HIV-1 viral load <200
- Prefrail or frail by Fried Frailty Phenotype
- Gait speed between 0.5-1.2 m/s
- Life expectancy of at least 2 years

**Primary endpoints**

- Safety and tolerability
- Change in gait speed (400 meter) at 12 weeks

**Secondary endpoints**

- Change in timed chair stands at 12 weeks
- Durability of change in physical function at 24, 36 weeks
- Senescent cell abundance (blood, adipose tissue)
- SASP composite biomarkers
- Cognitive function
- Frailty index
- Patient reported outcomes (quality of life)

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CROI 2023

# Trends in mortality in people living with HIV in an international cohort (RESPOND)

870

Erich Tusch[1], Annegret Pelchen-Matthews[2], Lars Peters[1], Amanda Mocroft[1,2], Daniel Elbirt[3], Cristiana Oprea[4], Huldrych Günthard[5], Cornelia Staehelin[6], Robert Zangerle[7], Colette Smith[8], Isabelle Suarez[9], Jörg Janne Vehreschild[9], Ferdinand Wit[10], Marianna Menozzi[11], Antonella d'Arminio Monforte[12], Vincenzo Spagnuolo[13], Christian Pradier[14], Christina Carlander[15], Paula Suanzes[16], Jan-Christian Wasmuth[17], Andrew Carr[18], Kathy Petoumenos[18], Nikoloz Chkhartishvili[19], Jonathan Carney[20], Bastian Neesgaard[1], Nadine Jaschinski[1], Lauren Greenberg[1], Sean R Hosein[21], Joel Gallant[22], Vani Vannappagari[23], Lital Young[24], Jens Lundgren[1], Lene Ryom[1,25], Joanne Reekie[1]

[1]CHIP, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, UK; [3]Allergy, Immunology and HIV Unit, Kaplan Medical Center, Rehovot, Israel; [4]Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania; [5]Swiss HIV Cohort Study (SHCS), University of Zurich, Zurich, Switzerland; [6]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland; [7]Austrian HIV Cohort Study (AHIVCOS), Medizinische Universität Innsbruck, Innsbruck, Austria; [8]The Royal Free HIV Cohort Study,Royal Free Hospital, University College London, London, United Kingdom; [9]University Hospital Cologne, Cologne, Germany; [10]AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, HIV Monitoring Foundation, Amsterdam, the Netherlands; [11]Modena HIV Cohort, Università degli Studi di Modena, Modena, Italy; [12]Italian Cohort Naive Antiretrovirals (ICONA), ASST Santi Paolo e Carlo, Milano, Italy; [13]San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, Milano, Italy; [14]Nice HIV Cohort, Université Côte d'Azur et Centre Hospitalier Universitaire, Nice, France; [15]Swedish InfCare HIV Cohort, Karolinska University Hospital, [16]Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Medicine Department, Universitat Autònoma de Barcelona, Bellaterra, Spain; [17]University Hospital Bonn, Bonn, Germany; [18]The Australian HIV Observational Database (AHOD), UNSW, Sydney, Australia; [19]Georgian National AIDS Health Information System (AIDS HIS), Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; [20]Frankfurt HIV Cohort Study, Johann Wolfgang Goethe-University Hospital, Frankfurt, Germany; [21]European AIDS Treatment Group (EATG), Brussels, Belgium; [22]Gilead Sciences, Foster City, California, USA; [23]ViiV Healthcare, Research Triangle Park, North Carolina, USA; [24]Merck Sharp & Dohme, Rahway, New Jersey, USA; [25]Department of Infectious Diseases 144, Hvidovre University Hospital, Copenhagen, Denmark

## RESPOND Cohort

## RESULTS

- 33,598 participants, 167,930 PYFU (median 4.8 years; IQR 3.1–8.0); 1700 (5.1%) died.
- Crude, all-cause mortality rate decreased over time.
  - 2012–13: 13.0/1000 PYFU (95%CI 11.8–14.4)
  - 2018–19: 8.6/1000 PYFU (95%CI 7.9–9.5)
- Median age at death increased over time:
  - 2012–13: 52 (IQR 45–62); 2018–19: 56 (IQR 48–65)
- Highest cause-specific crude mortality rate was due to non-AIDS defining malignancy (NADM); see Table 1.
- Age-adjusted Poisson regression showed decreasing mortality from 2012–13 to 2018–19 for deaths due to NADM, AIDS, cardiovascular disease (CVD), liver disease, and other causes, but not unknown/missing (see Figure 2).
- In multivariable analysis including all risk factors where $p<0.1$ in univariable analysis (Figure 1), the strongest predictors of all-cause mortality were poor immunologic/virologic status (current CD4 ≤350 cells/mm$^3$ + HIV viral load (VL) >200 cp/mL) vs. good immunologic/virologic status (CD4 ≥500 cells/mm$^3$ + VL <200 cp/mL) and other modifiable risk factors.

Figure 2: Age-standardized mortality rates (MR)

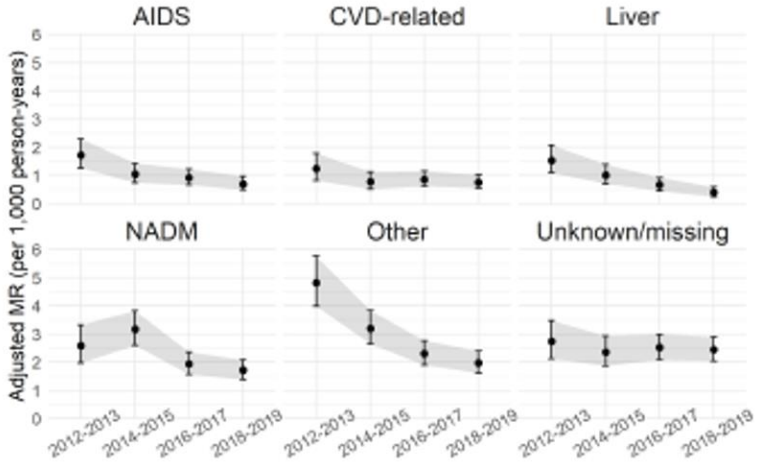


**Table 1: Cause-specific crude mortality rates (MR) per 1000 person-years**

| | N events | crude MR (95%CI) |
|---|---|---|
| NADM | 370 | 2.20 (1.98 - 2.44) |
| AIDS | 169 | 1.01 (0.85 - 1.16) |
| CVD | 142 | 0.85 (0.71 – 1.00) |
| Liver | 133 | 0.79 (0.66 - 0.94) |
| Other | 469 | 2.79 (2.55 - 3.06) |
| Unknown/missing | 417 | 2.48 (2.25 - 2.73) |

# Gracias

Próximo CROI 2024

**Denver**