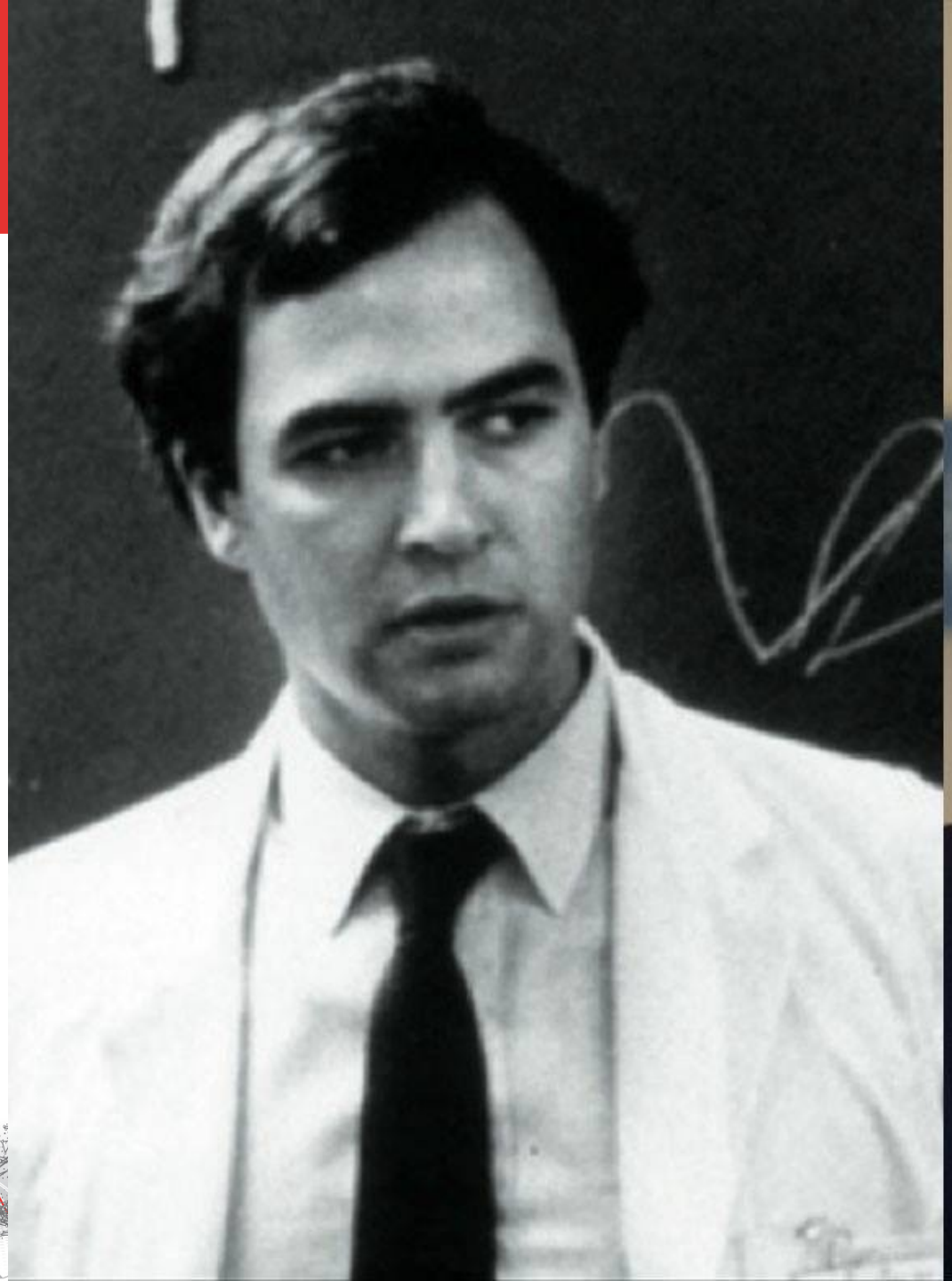
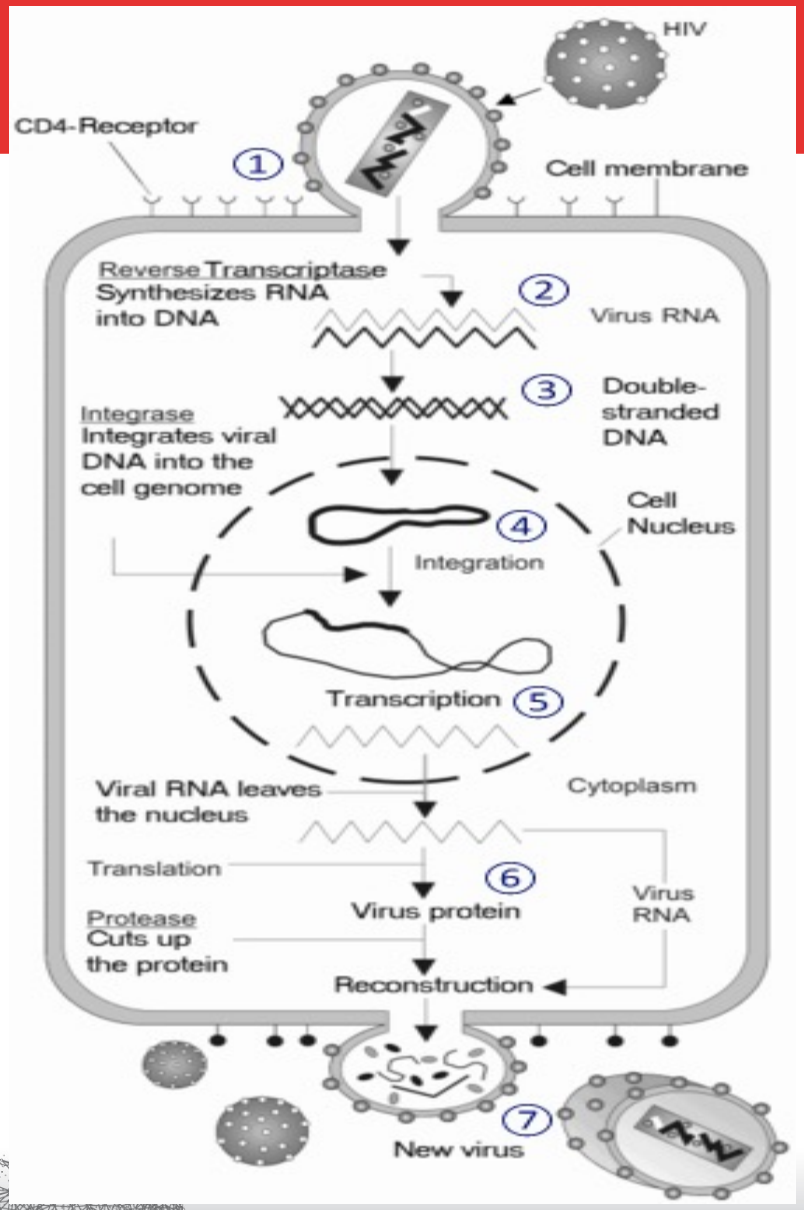
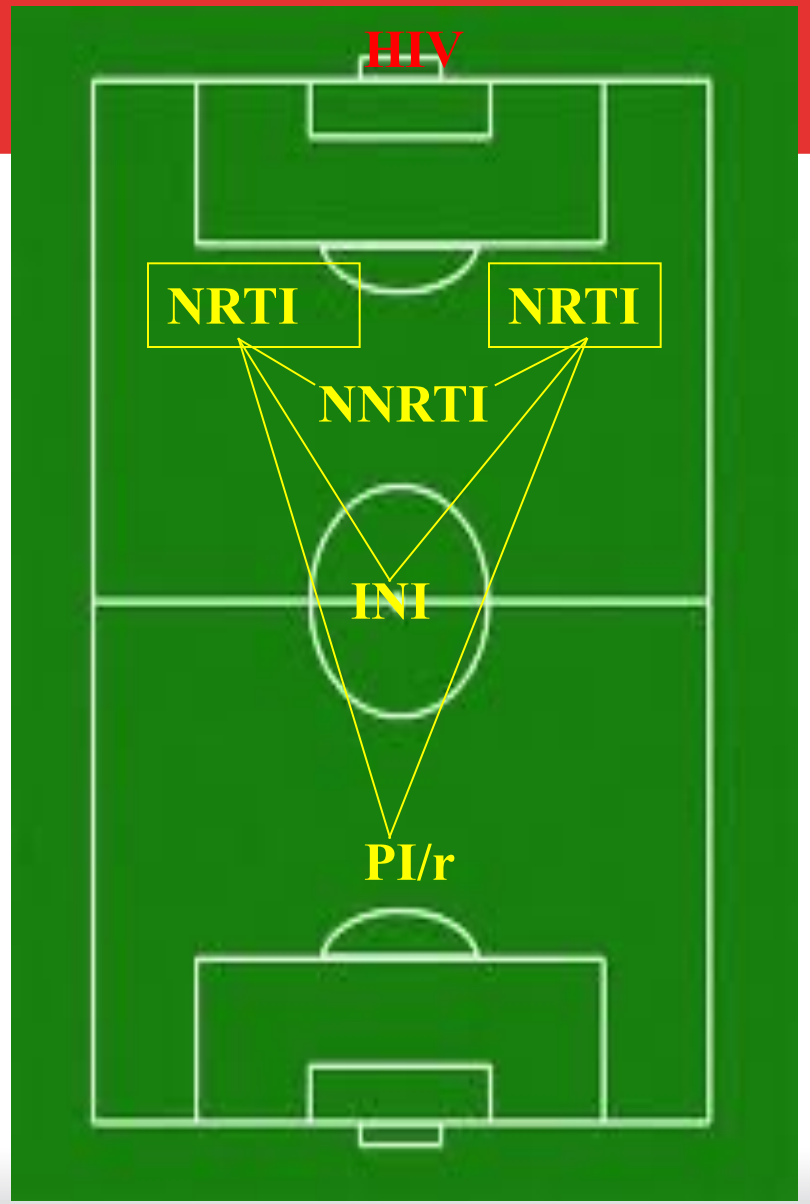
HIV e AIDS



ert
op HIV
REAL TIME
10 ANNI
Post-CROI 2022


HIV
CD4-Receptor
1
Cell membrane
Reverse Transcriptase
Synthesizes RNA
into DNA
2
Virus RNA
3
Double-
stranded
DNA
Integrase
Integrates viral
DNA into the
cell genome
Cell
Nucleus
4
Integration
Transcription
5
Viral RNA leaves
the nucleus
Cytoplasm
Translation
6
Virus protein
Virus
RNA
Protease
Cuts up
the protein
Reconstruction
7
New virus


HIV
NRTI
NRTI
NNRTI
INI
PI/r

Epidemiologia dell'infezione da HIV in era COVID-19

CORRIERE DELLA SERA

Ora è chiusa tutta l'Italia

la Repubblica

Tutti in casa

LA STAMPA

24 ORE

Effetto virus e petrolio a picco, Borse ko
Tutta Italia zona arancione e deficit al 2,9%

il Fatto Quotidiano

LA GRANDE FUGA: 20MILA IN 2 GIORNI

ristora
INSTANT DRINKS

LaVerità

ECCO IL CONTO DA PAGARE

Paura per il Sud, verso misure più dure «Rossa» tutta l'Italia

Libero

LE ULTIME PAROLE FAMOSE

QUELLI CHE DICEVANO: è poco più di un'influenza

il Giornale

Altri 1.598 infetti e 97 morti. Respira il paziente 1

SI CHIUDE TUTTO
(E GUARDATE QUESTA FOTO)

Zona rossa da Nord a Sud. La Borsa crolla: -11%
Carceri, rivolte ed evasioni e scappa anche il ministro

Avvenire

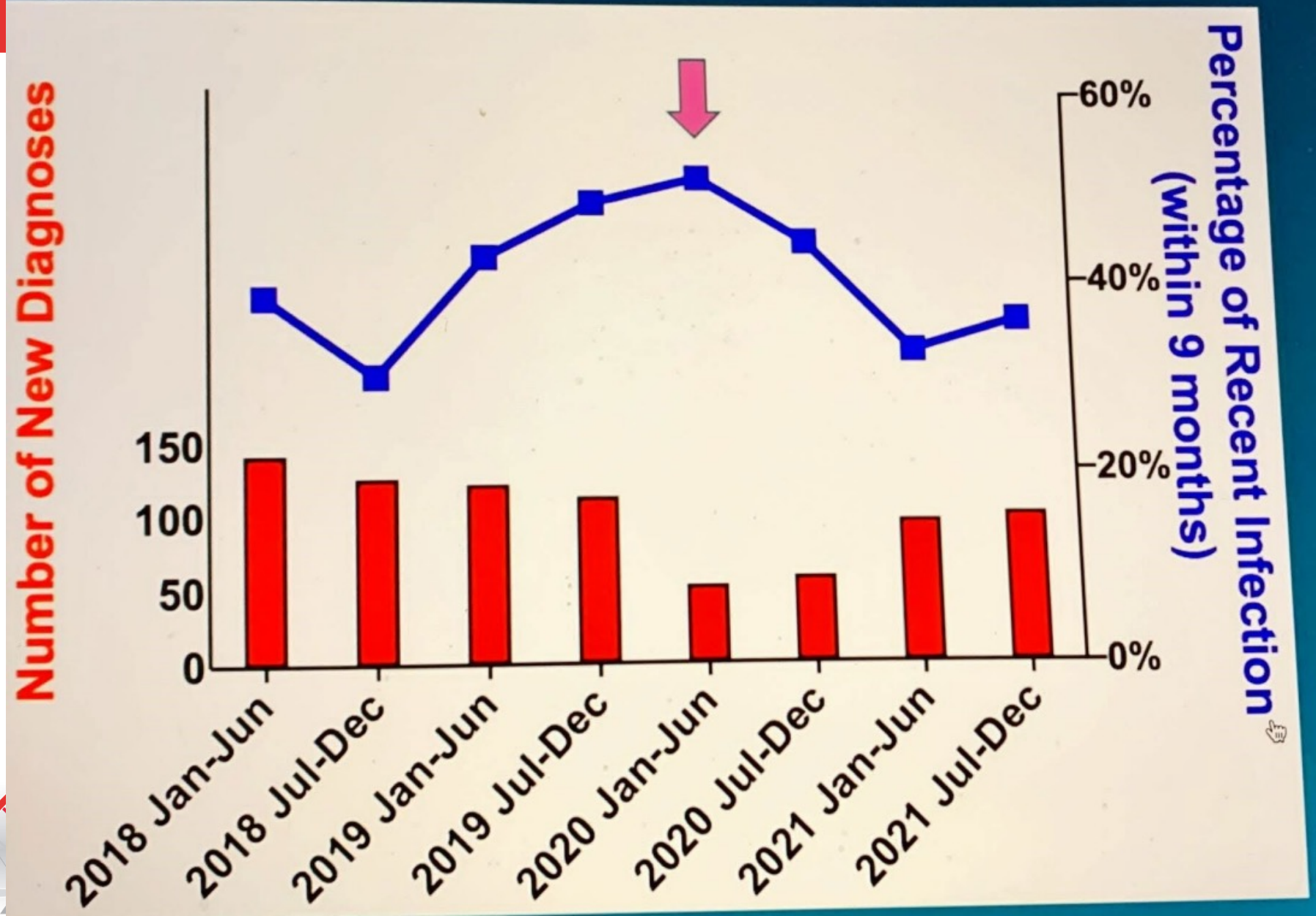
Totale protezione

il manifesto

Carceri in rivolta, il virus cova da tempo

Tutti a casa

New Diagnoses and Percentage of Recent Infection Varied Significantly over Four Years (2018-2021) of Screening in NC



Early 2020:
- lowest number of diagnoses
- highest % of recent infection
- related to COVID-19 pandemic

Late 2020 to 2021:
- Decline in the % of recent infection
- Return to broader HIV-1 testing and diagnosis

HIV

Si sottolinea che i dati relativi al 2020 possono aver risentito dell'emergenza COVID-19.

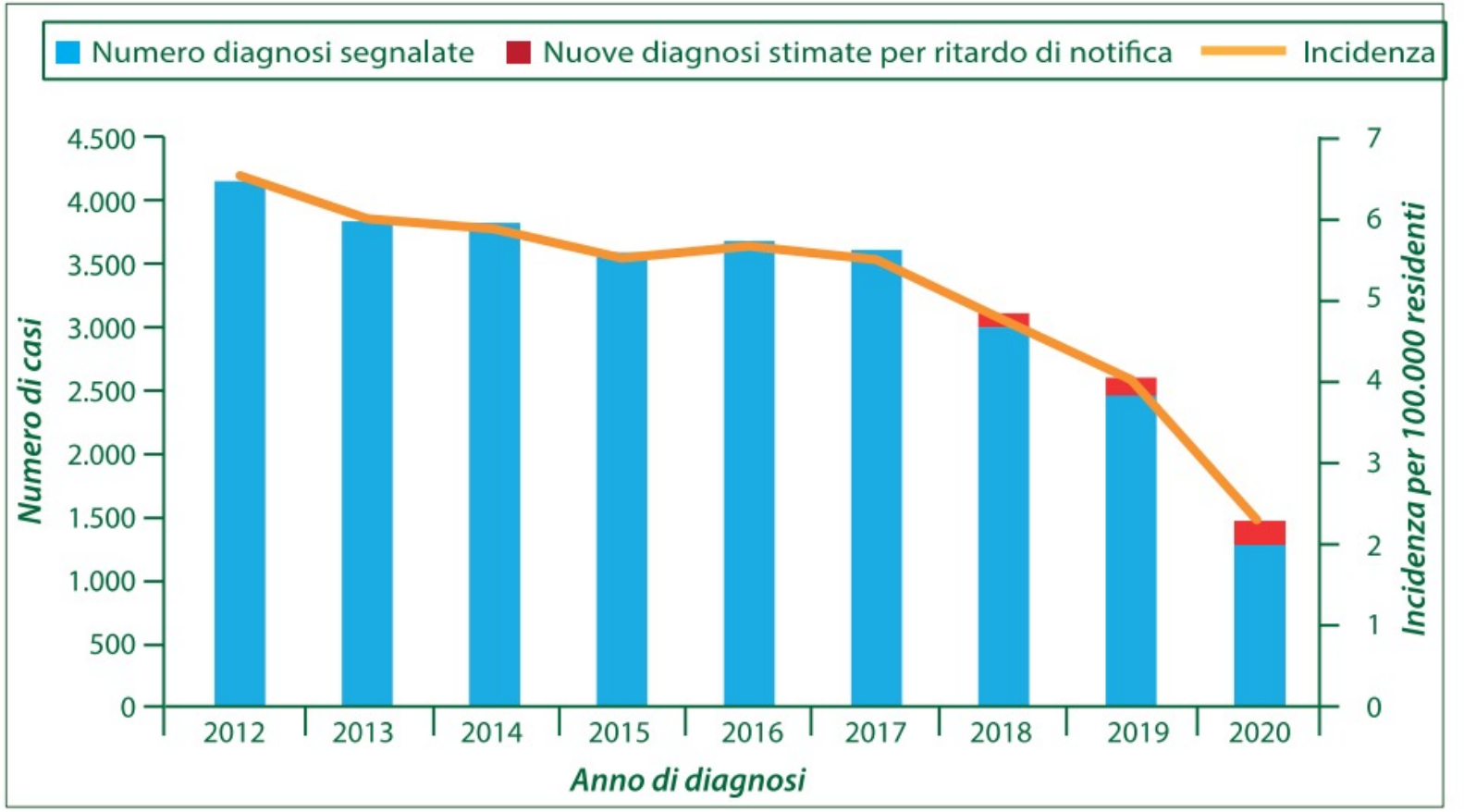
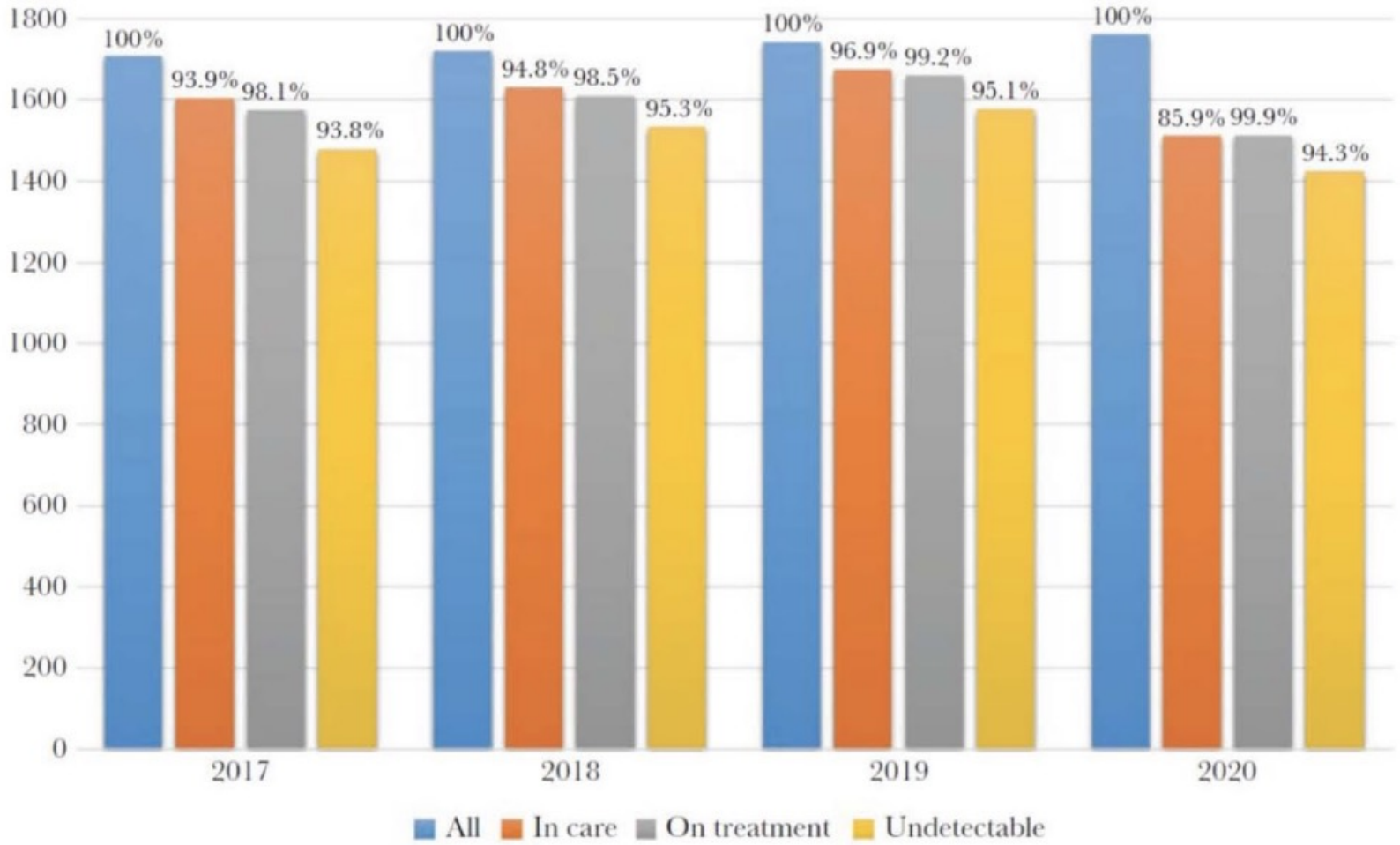


Figura 1 - Numero di nuove diagnosi di infezione da HIV e incidenza corrette per ritardo di notifica (2012-2020)

Impact of COVID-19 on HIV Continuum of Care in Modena Province



Guaraldi 2021

Delivery of care

Multi-month supplies of HIV medications – recommended during lockdowns – are not authorised in many countries

Roger Pebody | 12 May 2020

More news

Delivery of care

Is telemedicine for HIV here to stay?

8 June 2020

Delivery of care

Multi-month supplies of HIV medications – recommended during lockdowns – are not authorised in many countries

12 May 2020

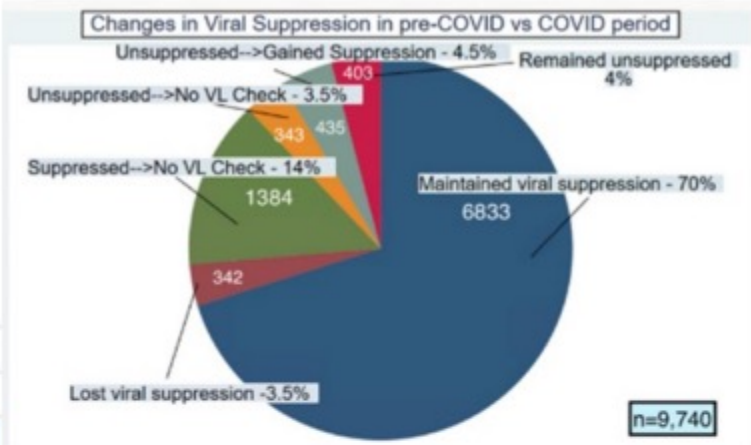
Coronavirus

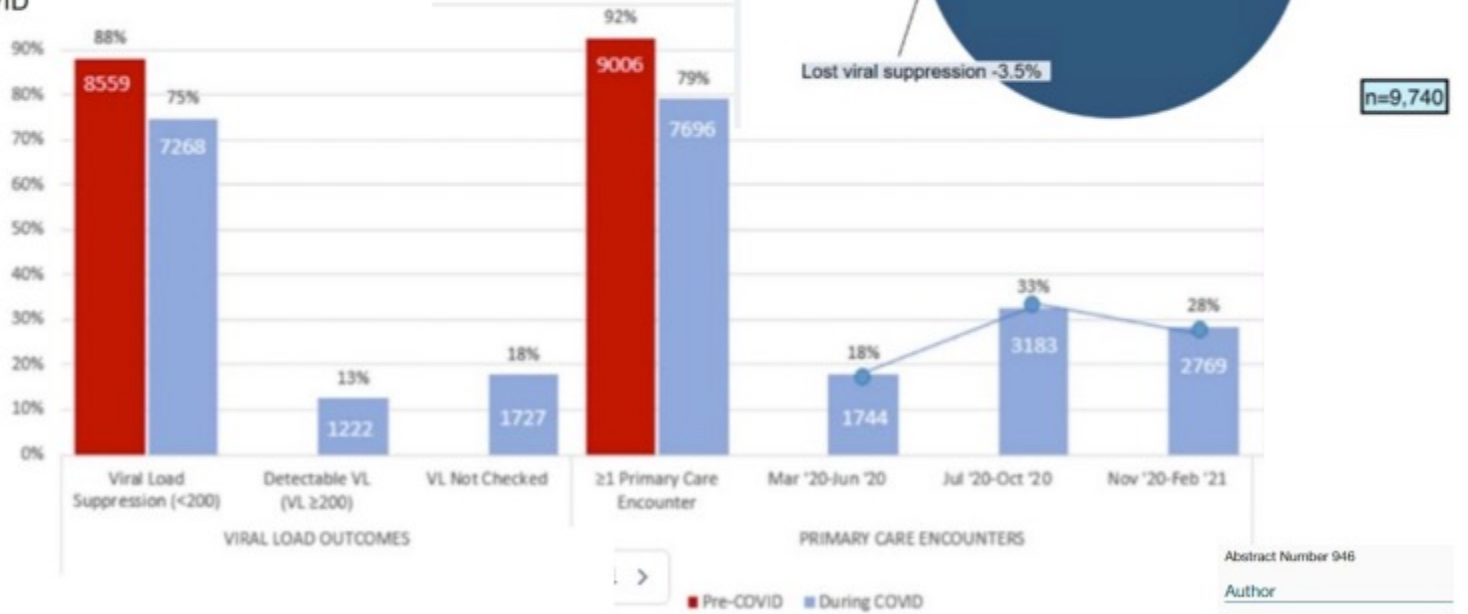
COVID-19 rapidly reshaping

SCOSTAMENTO DALLA PUNTUALITÀ DEI PAZIENTI HIV + SEGUITI PRESSO L'AMBULATORIO DEL POLICLINICO SAN MARTINO

Busin V, 2021 unpublished

- 18% of patients had no VL monitoring during the COVID period
- A substantial portion of patients (15%) were lost to follow-up; i.e. not engaged in care nor monitored for VLS
- We saw a drop in primary care visits, while ART prescription rates were unchanged
- Black and Hispanic patients were at particular risk of rebound viremia in the COVID period
- Factors including age <35, being male or a transgender woman, Black or Hispanic race, and HIV risk factor of injection drug use or heterosexual sex were associated with viral non-suppression or no VL monitoring during COVID



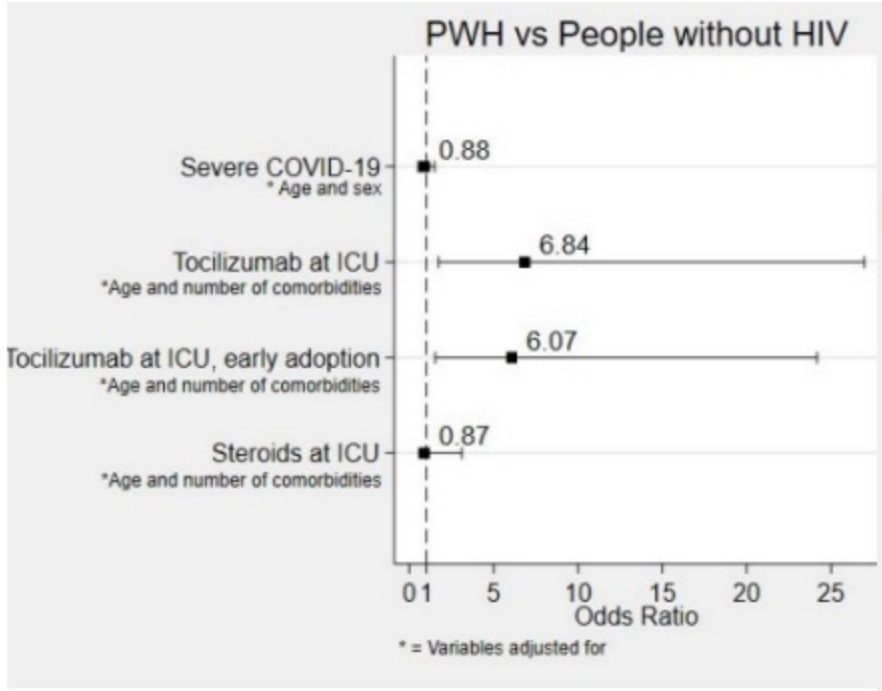


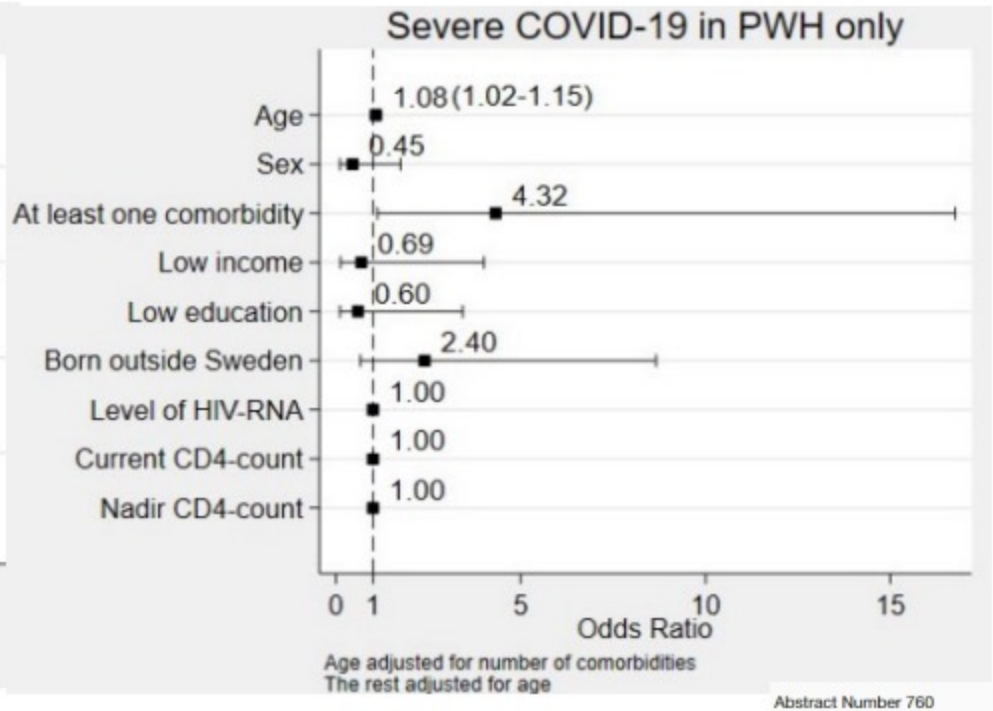
Abstract Number 946

Author

Shaoli Chaudhuri
Icahn School of Medicine at Mount Sinai

People living with HIV (PWH) in Sweden with **well-treated** HIV-infection hospitalized with COVID-19 did **not have higher odds of severe COVID-19** compared to HIV-negative individuals. (121 PWH)





Abstract Number 760

Author

Isabela Möller
Karolinska Institutet

Factors associated to COVID-19 severity in 155 PLWH

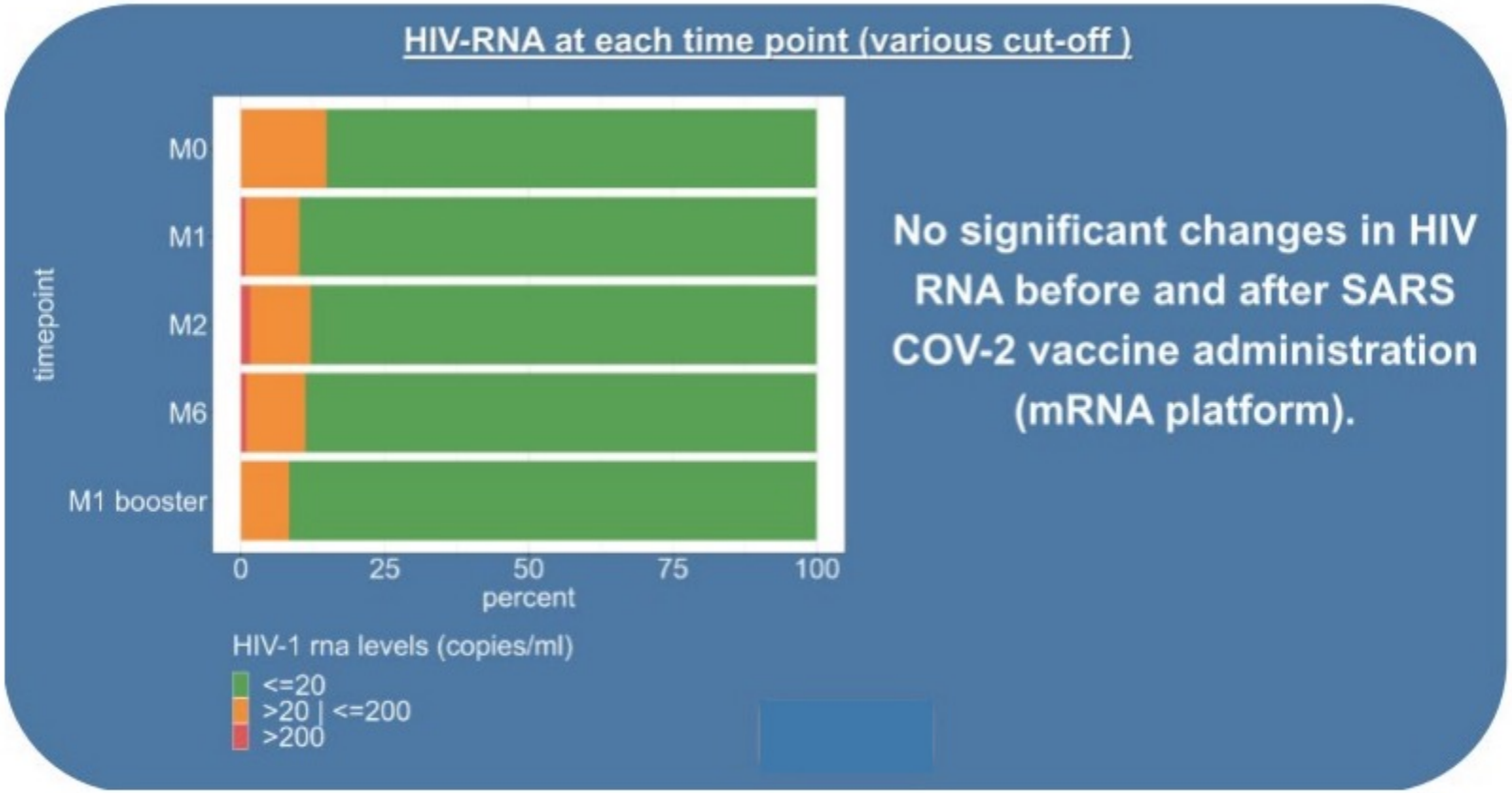
Variable	NIH Classification				P	P
	Asymptomatic	Mild	Moderate	Severe	univariate	multivariate
number	32 (20.6%)	78 (50.3%)	28 (18.1%)	17 (11.0%)	-	-
Age (years)	56 (52-59)	52 (50-54)	54 (51-57)	62 (58-67)	0.001	0.002
Diabetes No Yes	28 (87.5%) 4 (12.5%)	74 (94.9%) 4 (5.1%)	27 (96.4%) 1 (3.6%)	12 (70.6%) 5 (29.4%)	0.009	0.019
Hypertension No Yes	26 (81.3%) 6 (18.8%)	67 (85.9%) 11 (14.1%)	20 (71.4%) 8 (28.6%)	8 (47.1%) 9 (52.9%)	0.004	0.175
Cardiovascular diseases No Yes	24 (75.0%) 8 (25.0%)	76 (97.4%) 2 (2.6%)	23 (82.1%) 5 (17.9%)	11 (64.7%) 6 (35.3%)	0.001	0.240
Number of co-morbidities	1.59 (1.0-2.1)	1.01 (0.7-1.3)	1.32 (0.8-1.8)	2.47 (1.3-3.6)	0.002	0.690

Number and (percentages)
Mean and (95%CI)

Factors associated to the risk of death in 155 PLWH

Variable	Alive	Deceased	P univariate	P multivariate
Number	149 (96.1%)	6 (3.9%)	-	-
Number of CD4/ml (last count)	852 (791-915)	502 (421-584)	0.027	0.024
Number of co-morbidities	1.26 (1.0-1.5)	3.50 (1.5-5.5)	< 0.0001	0.002
Age (years)	54 (52-55)	67 (61-74)	< 0.0001	0.206
Diabetes No Yes	138 (92.6%) 11 (7.4%)	3 (50.0%) 3 (50.0%)	0.010	0.120
Hypertension No Yes	119 (79.9%) 30 (20.1%)	2 (33.3%) 4 (66.7%)	0.021	0.557
Cardiovascular diseases No Yes	131 (87.9%) 18 (12.1%)	3 (50.0%) 3 (50.0%)	0.033	0.644
Dyslipidemia No Yes	130 (87.2%) 19 (12.8%)	3 (50.0%) 3 (50.0%)	0.038	0.427
Renal No Yes	141 (94.6%) 8 (5.4%)	4 (66.7%) 2 (33.3%)	0.049	0.948
CDC A3:B3:C3	41 (27.5%)	4 (66.0%)	0.001	0.127

Number and (percentages)
Mean and (95%CI)



No significant changes in HIV RNA before and after SARS COV-2 vaccine administration (mRNA platform).

Abstract Number 941

Author

CROI 2022

Chiara Fedeli
Hospital of Geneva

Nuovi farmaci e strategie

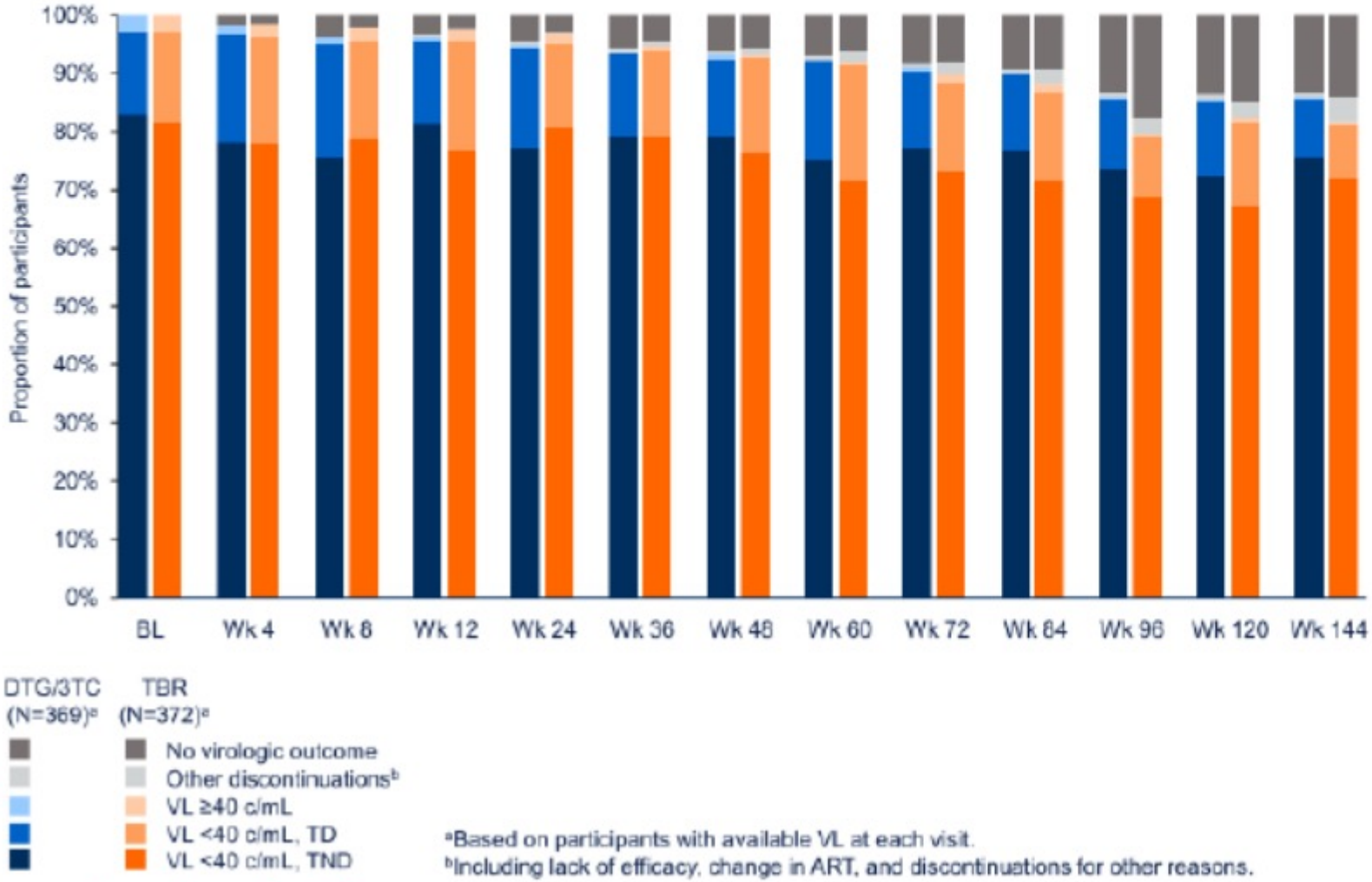
LOW-LEVEL HIV-1 REPLICATION FOR DTG/3TC VS TAF-BASED REGIMEN IN TANGO THROUGH WEEK 144

Ruolan Wang,[1] Nisha George,[2] Mounir Ait-Khaled,[3] Andrew Tomlinson,[4] James Oyee,[4] Thomas Lutz,[5] Olayemi Osiyemi,[6] Miguel Górgolas,[7] Riya Moodley,[8] Brian Wynne,[1] Myooran Sithamparanathan,[9] Mark Underwood[1]

[1]ViiV Healthcare, Research Triangle Park, NC, USA; [2]GlaxoSmithKline, Bangalore, India; [3]ViiV Healthcare, Brentford, UK; [4]GlaxoSmithKline, Brentford, UK; [5]Infektio Research, Frankfurt, Germany; [6]Triple O Research Institute PA, West Palm Beach, FL, USA; [7]Jiménez Díaz Foundation University Hospital, Madrid, Spain

Post-CROI 2022

Figure 2. Summary of Proportion of Participants With VL <40 c/mL and TND, VL <40 c/mL and TD, and VL ≥40 c/mL by Visit



[a]Based on participants with available VL at each visit.
[b]Including lack of efficacy, change in ART, and discontinuations for other reasons.

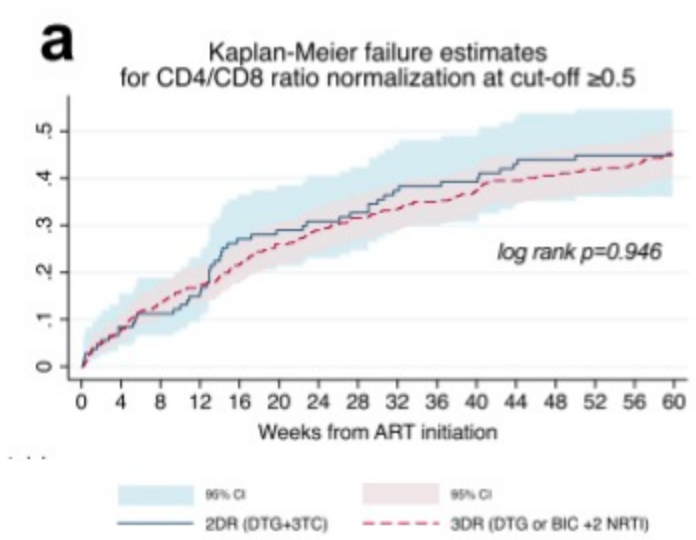
Table 2. Summary of Participants With Elevated VL Categories Through Week 144

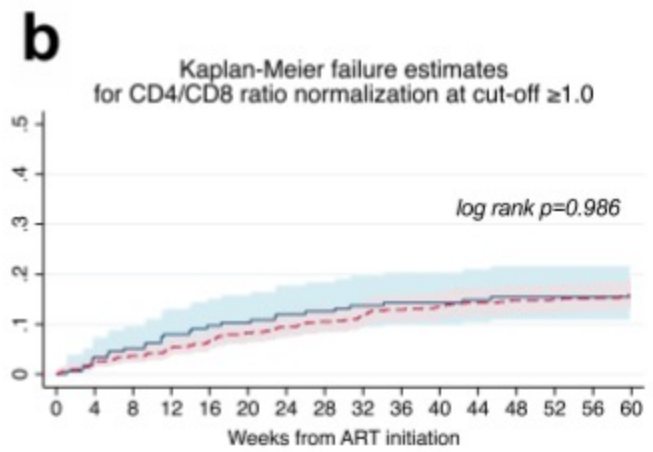
Elevated VL categories for participants in the ITT-E population	DTG/3TC FDC (N=369) n (%)	TAF-based regimen (N=372) n (%)
1. Participants with VLs between 50 to <200 c/mL and no VL ≥200 c/mL	**21 (6%)**	**32 (9%)**
1a. VLs between 50 to <200 c/mL with adjacent values <50 c/mL ("blips")	18 (5%)	26 (7%)
1b. ≥2 consecutive VLs between 50 to <200 c/mL	3 (<1%)	6 (2%)
2. Participants with at least one VL ≥200 c/mL	**7 (2%)**	**10 (3%)**
2a. A single VL ≥200 c/mL and no 2 consecutive VLs ≥50 c/mL	7 (2%)	6 (2%)
2b. ≥2 consecutive VLs ≥50 c/mL with at least one VL ≥200 c/mL	0	4 (1%)[a]
Total (all categories)	**28 (8%)**	**42 (11%)**

Conclusions

- The proportions of participants with VL <40 c/mL and TND by visit were high and comparable between treatment arms.
- Similar proportions of participants across both arms maintained post-baseline TND at all visits through Week 144 and >90% of participants on DTG/3TC with TND at baseline never had a VL ≥40 c/mL.
- Using the more stringent VL <40 c/mL and TND threshold, DTG/3TC 2DR shows no evidence of being less effective than TAF-based 3DR.
- These long-term virology data continue to demonstrate the high potency and durability of DTG/3TC compared with 3DR in maintaining viral suppression.

2DR vs 3DR INI based regimens





Abstract Number 482

Author

Javier Martínez-Sanz
Hospital Universitario Ramón y Cajal

Capsid is Critical at Multiple Stages of HIV Replication Cycle

- The HIV capsid is transported intact along microtubules to the site of nuclear import
- The capsid passes through the nuclear pore intact
- Reverse transcription is completed within an intact capsid in the nucleus
- Capsid disassembles prior and near the site of integration

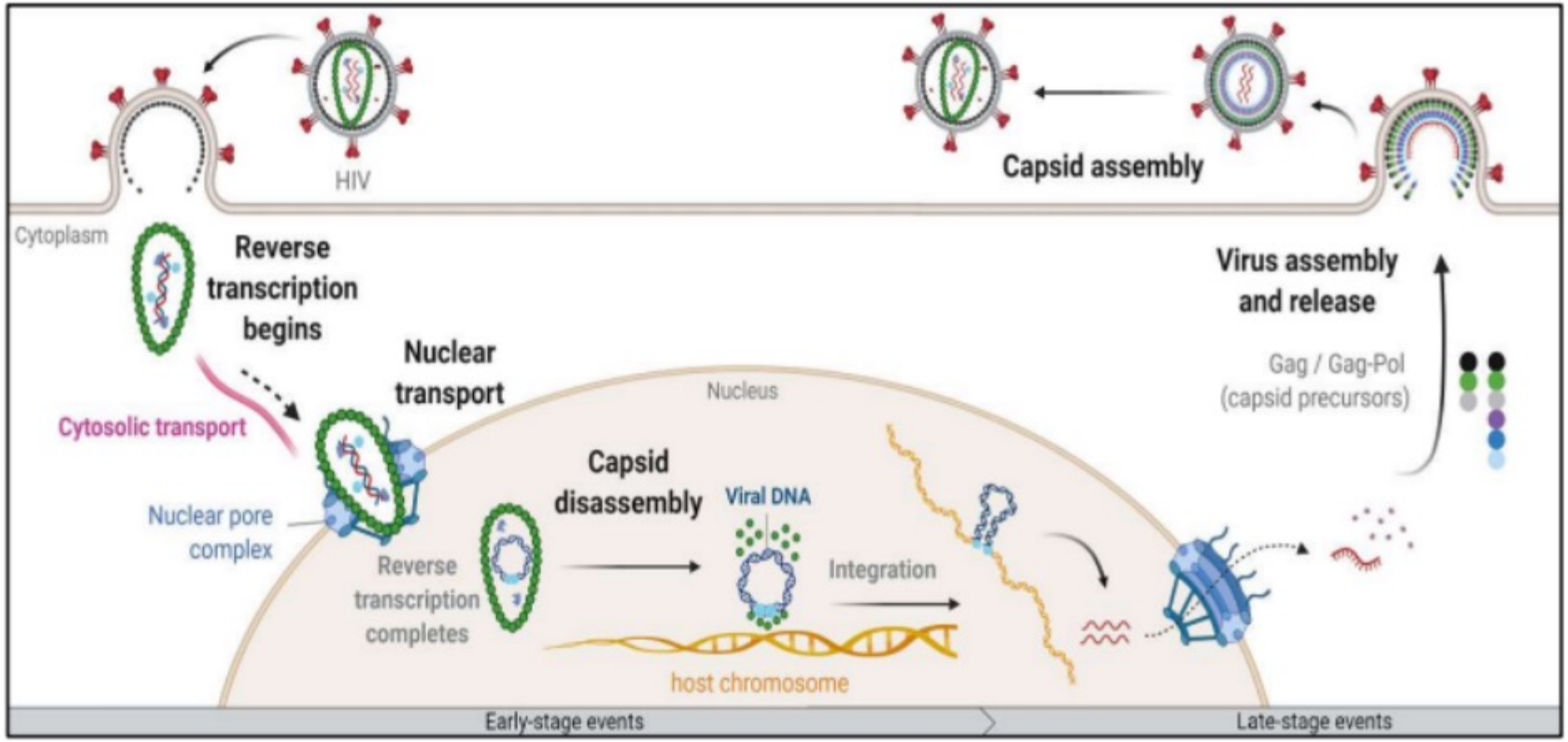
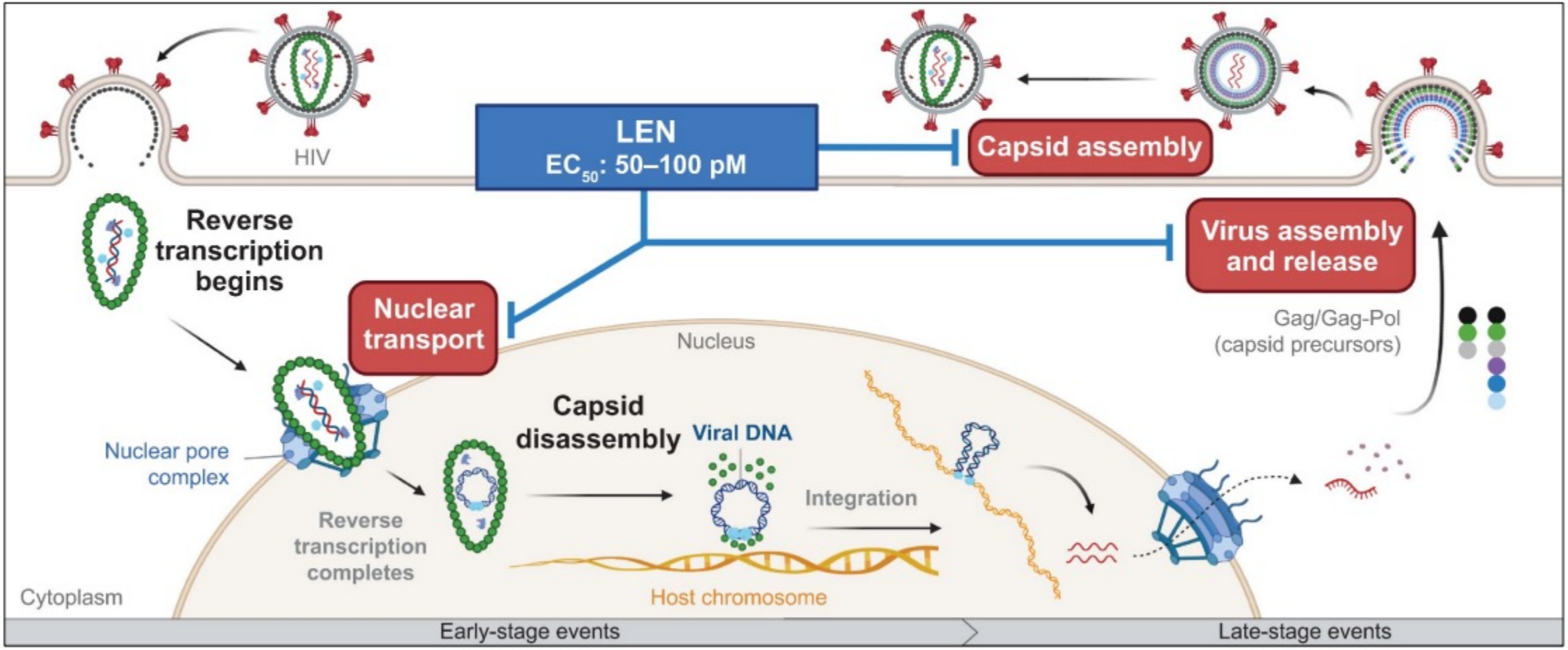
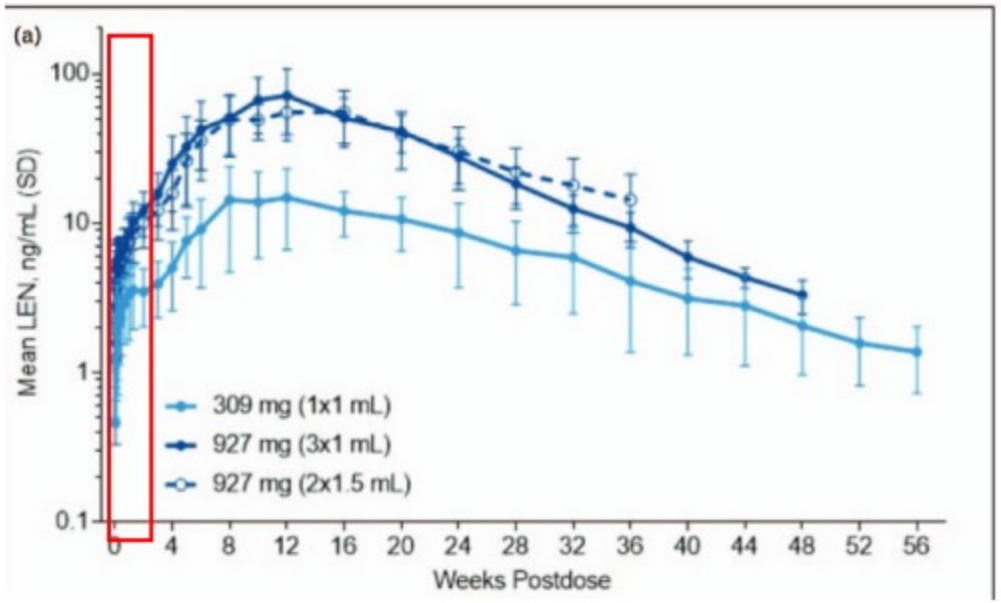


Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

Lenacapavir (LEN; GS-6207) Targets Multiple Stages of HIV Replication Cycle[1,2]

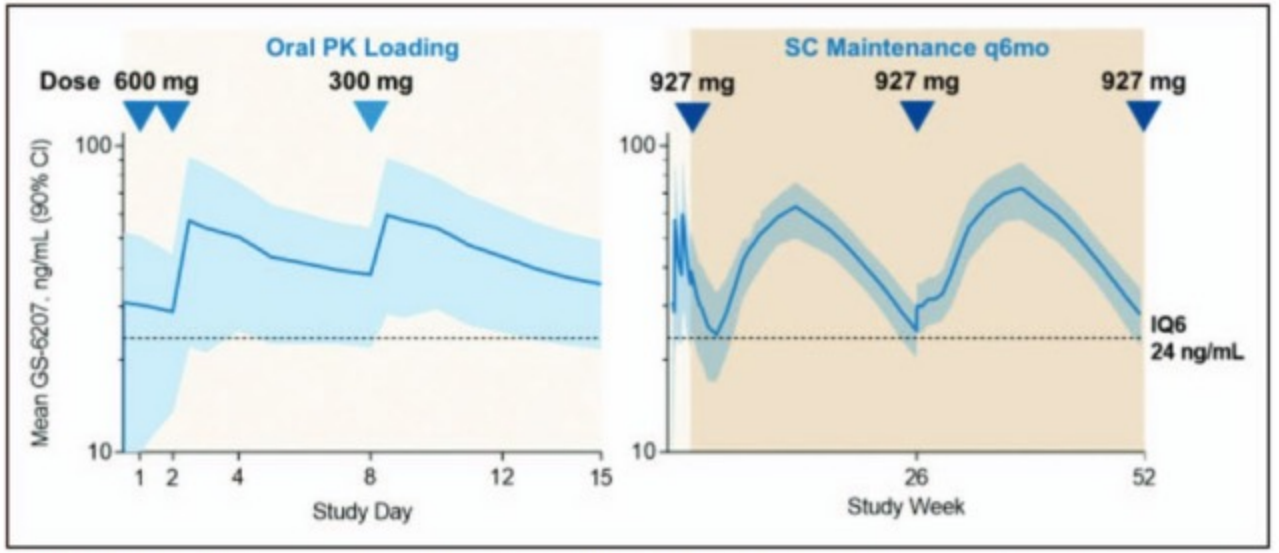


EC_{50}, half-maximal effective concentration; Gag, group antigens; Pol, polyprotein.



- After a single, 927 mg subcutaneousdose of lenacapavir, target plasma concentrations are sustained for at least 6 months, corresponding to mean inhibitory quotient of at least 6 (i.e. six-fold higher than the protein-adjusted EC95).
- However, **a slow initial rise** after administration of subcutaneous lenacapavir in the first few weeks was noted, leading to consideration of **initial pharmacokinetic loading with oral lenacapavir**

Oral $t_{1/2}$ 10-12 days



SC $t_{1/2}$ 8-12 weeks

FIGURE 3. Predicted lenacapavir pharmacokinetics for phase 2/3 oral and subcutaneous combination regimens in healthy volunteers. Adapted from [10▪].

Hadas Dvory-Sobol, Curr Opinion HIV 2022

Lenacapavir as part of a Combination Regimen in Treatment-Naïve People with HIV: Week 54 Results

Samir K. Gupta,[1] James Sims,[2] Cynthia Brinson,[3] Frederick A. Cruickshank,[4] Godson Oguchi,[5] Javier Morales,[6] Theo Hodge,[7] Craig Dietz,[8] Angela S. Liu,[9] Laurie VanderVeen,[9] Hadas Dvory-Sobol,[9] Martin S. Rhee,[9] Jared M. Baeten,[9] Ellen Koenig[10]

[1]Indiana University School of Medicine, Indianapolis, IN, USA; [2]St. Hope Foundation, Bellaire, TX, USA; [3]Central Texas Clinical Research, Austin, TX, USA; [4]Rosedale Infectious Diseases, Huntersville, NC, USA; [5]Midland Florida Clinical Research Center, LLC, Deland, FL, USA; [6]Clinical Research Puerto Rico Inc, San Juan, Puerto Rico, USA; [7]Washington Health Institute, Washington DC, USA; [8]Kansas City Care Health Center, Kansas City, MO, USA; [9]Gilead Sciences Inc., Foster City, CA, USA; [10]Instituto Dominicano de Estudios Virológicos, Santo Domingo, Dominican Republic

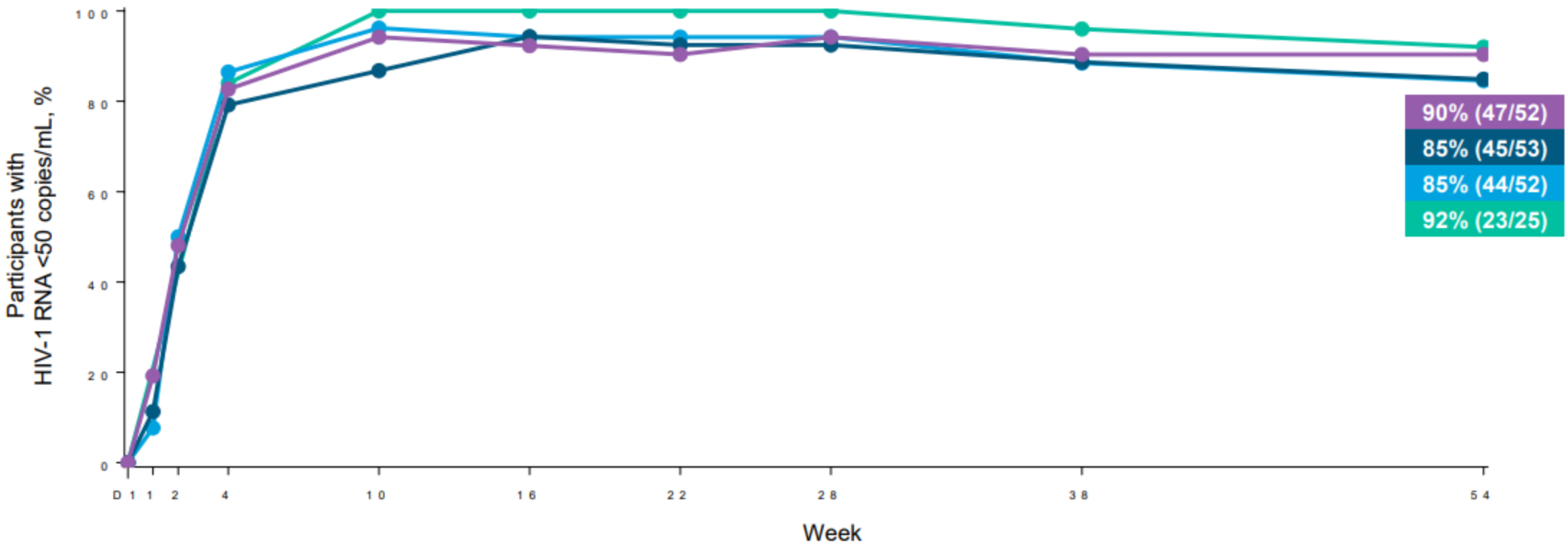
CROI 2022

Participants with HIV-1 RNA <50 copies/mL by Visit

Missing = Failure (On Treatment)

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF

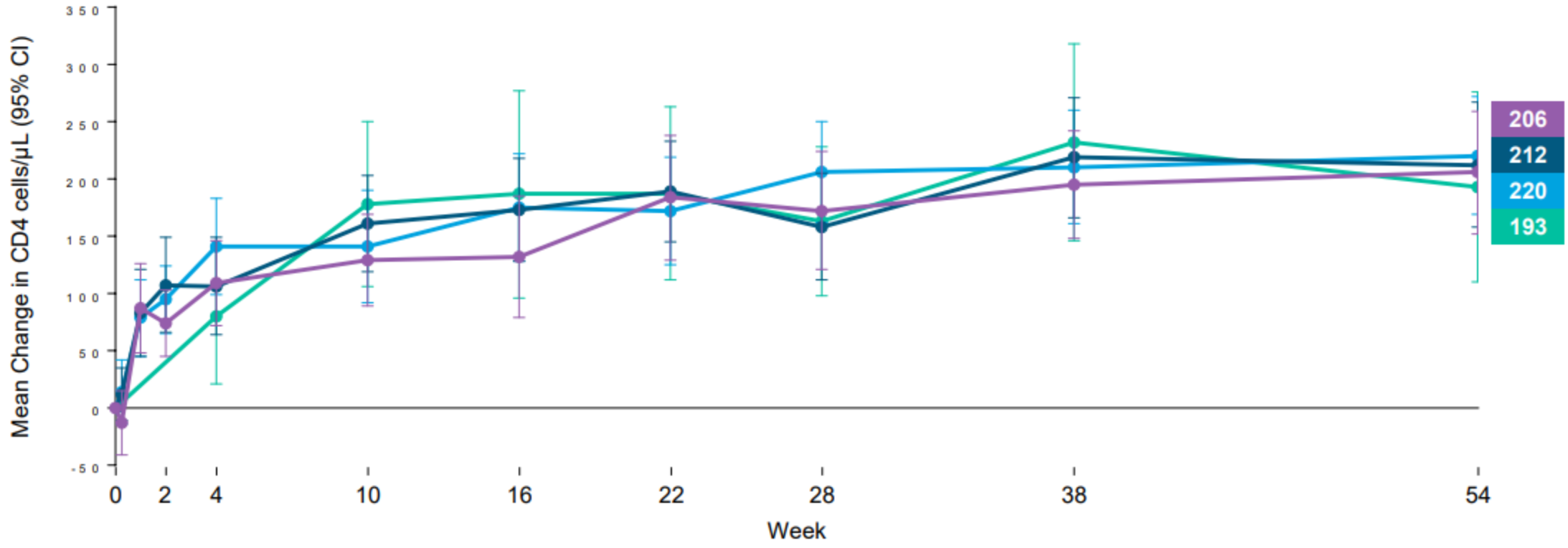


Samir K. Gupta et al. vCROI 2022. Abstract#138

Changes in CD4

Calibrate

TG 1: LEN SC + F/TAF to LEN SC + TAF
TG 2: LEN SC + F/TAF to LEN SC + BIC
TG 3: LEN QD + F/TAF
TG 4: B/F/TAF



- Baseline CD4 of the overall study population: median 437 cells/µL

Samir K. Gupta et al. vCROI 2022. Abstract#138

Injection Site Reactions

ISR Types*	After 1st SC Dose at Week 1 n=103†	After 2nd SC dose at Week 26 n=95†	Median duration (days)
Swelling	14%	12%	11
Erythema	14%	18%	5
Pain	15%	9%	4
Nodule	11%	8%	195
Induration	9%	6%	202

- Mostly Grade 1 or 2 ISRs
  - One Grade 3 ISR (nodule) after the second SC dose
- Three participants discontinued due to ISRs:
  - Two due to induration (both Grade 1, after the first SC dose)
  - One due to erythema and swelling (Grade 1, after the second SC dose)

*Includes those >5% at both Weeks 1 and 26; †TG 1+2 (ie, those who received ≥1 dose of SC LEN and still on study or last study date in 2-week interval).

Samir K. Gupta et al. vCROI 2022. Abstract#138

LONG ACTING LENACAPAVIR PROTECTS AGAINST INTRAVENOUS CHALLENGE WITH SIMIAN-TROPIC HIV

00860

Adrienne E. Swanstrom[1], Bing Lu[2], Kelly Wang[2], Jim Zheng[2], Matthew W. Breed[3], Kristin E. Killoran[3], Joshua Kramer[3], Jorden L. Welker[1], Paul D. Bieniasz[4], Theodora Hatziioannou[4], Robert J. Gorelick[1], Wade Blair[2], Stephen R. Yant[2], Jeffrey D. Lifson[1], **Gregory Q. Del Prete[1]**

[1]AIDS and Cancer Virus Program, and [3]Laboratory Animal Sciences Program, Frederick National Laboratory for Cancer Research, Frederick, MD, USA; [2]Gilead Sciences, Foster City, CA, USA; [4]Laboratory of Retrovirology, Rockefeller University, New York, NY, USA

Background

- Daily pre-exposure prophylaxis (PrEP) is highly effective but dependent on adherence.
- Lenacapavir (LEN) is a potent first-in-class HIV capsid (CA) inhibitor with long-acting pharmacokinetics (PK), making it attractive for PrEP[1].
- A less potent LEN analogue, GS-CA1, has recently shown efficacy in repeat SHIV rectal and vaginal challenge models in rhesus macaques[2,3].
- LEN and GS-CA1 both effectively inhibit HIV capsid nuclear import, virion assembly, and proper capsid core formation[1,4].
- We previously derived a simian-tropic HIV-1 infectious clone (stHIV-A19) that encodes HIV-1 CA and replicates to high titers in pigtail macaques (PTMs)[5,6].

stHIV-A19 CA Sequence

*HIV-1 CA residues associated with LEN resistance (L56, N57, M66, Q67, K70, N74, T107) are highlighted in yellow, with those distinct from NL4-3 and stHIV-A19 highlighted in cyan

Objectives

- To comparatively evaluate LEN antiviral potency in vitro against stHIV, HIV-1, and SIVmac239
- To evaluate PK and efficacy of subcutaneous (SC) LEN PrEP in PTMs against a high-dose intravenous (IV) stHIV challenge

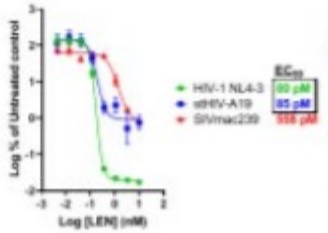
Methods

- LEN potency against stHIV-A19, HIV-1 NL4-3, and SIVmac239 was compared in SupT1-CCR5 cells (qRT-PCR readout 7 dpi). LEN potency against stHIV-A19 was then determined in PTM PBMCs (RT readout 7 dpi). After correcting for PTM plasma protein binding by competitive equilibrium dialysis, a plasma-adjusted (PA)-EC_{95} for LEN was derived.
- LEN PK was assessed in PTMs receiving two subcutaneous (SC) doses of LEN 6 weeks apart (15 mg/kg x 2, n=3; 50 mg/kg x 2, n=3). LEN plasma levels were determined by LC-MS.
- Prior to a single IV challenge with 10^5 infectious units of stHIV-A19, naïve PTMs received either: (1) a single SC injection of LEN (25 mg/kg, 30 days pre-challenge, n=3), (2) a single SC vehicle injection (30 days pre-challenge, n=4), or (3) 7 daily doses of a 3-drug control regimen[7] (TDF/FTC/DTG, starting 3 days pre-challenge, n=4). Plasma stHIV RNA (vRNA) and stHIV DNA (vDNA) in PBMCs were monitored by qRT-PCR and qPCR, respectively.

Results

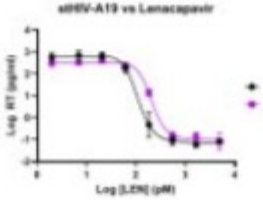
1. LEN Potency against stHIV In Vitro

SupT1-CCR5+ cells



- stHIV-A19 and HIV-1 equally sensitive to LEN
- LEN more potent against stHIV than SIVmac239

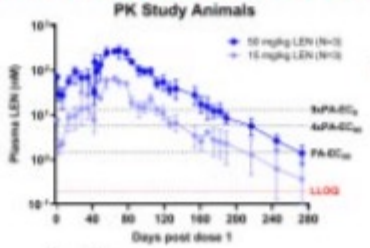
PTM PBMC



- LEN EC_{95} vs stHIV in PTM PBMCs = 150 pM
- LEN PA-EC_{95} = 1.46 nM

2. LEN Pharmacokinetics in PTMs

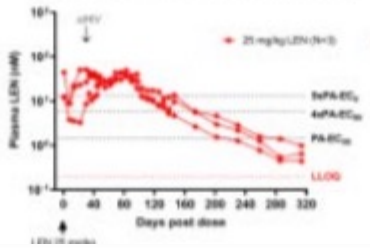
PK Study Animals



- Mean plasma LEN concentrations maintained above PA-EC_{95} for >145 and >200 days after 2nd 15 mg/kg and 50 mg/kg dose, respectively

*Mean ± range of measured values shown

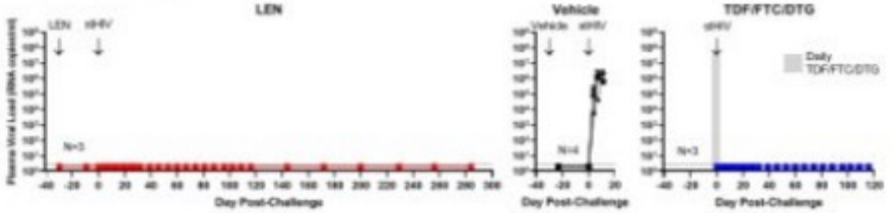
LEN PrEP Animals in IV Challenge Study



- Mean plasma LEN concentrations exceeded target protective levels (4x PA-EC_{95}) by day 1 post dose and at the time of challenge

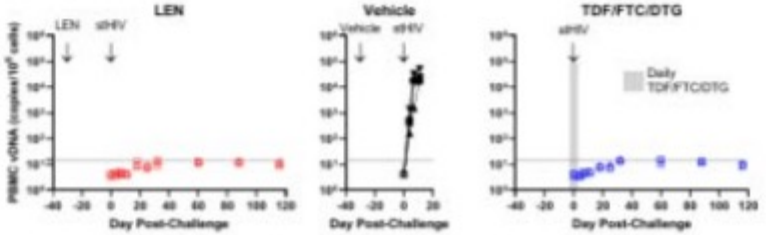
3. LEN PrEP vs IV stHIV Challenge

Plasma Viral Loads



*LOD = 2.8 vRNA copies/ml (dashed line)

vDNA in PBMC



*LOD = 15 vDNA copies/10^6 cells (dashed line); open symbols = no vDNA detected

- No evidence of infection in LEN or three-drug control animals (>8 months of follow-up for LEN animals)
- All 4 vehicle control animals infected

4. LEN Safety in PTMs

- No abnormalities or significant changes in complete blood counts (CBC) or blood serum chemistries in animals that received LEN injections
- Mild to moderate injection site reactions, which resolved without intervention, observed in some animals following some LEN injections or vehicle control injections

Conclusions

- A single subcutaneous LEN injection effectively prevented simian-tropic HIV infection in a stringent, high dose intravenous challenge model
- These findings highlight the utility of this stHIV/PTM model and support the ongoing clinical development of long-acting LEN for PrEP

TRANSFORMATION OF DOLUTEGRAVIR INTO A YEAR-LONG PARENTERAL PRODRUG FORMULATION

Suyash S. Deodhar[1†], Brady J. Sillman[1†], Aditya N. Bade[1], JoEllyn M. McMillan[1], Nagsen Gautam[2], Brandon Hanson[1], Bhagya L. Dyavar Shetty[1], Adam Szlachetka[3], Morgan Johnston[1], Michellie Thurman[1], Daniel J. Munt[4], Alekha K. Dash[4], Milica Markovic[1], Arik Dahan[5], Yazen Alnouti[2], Bhavesh D. Kevadiya[1], Siddappa N. Byrareddy[1], Samuel M. Cohen[6], Benson J. Edagwa[1,3*], and Howard E. Gendelman[1,2,3*]

Hydrophobic prodrug nanocrystals provide plasma DTG levels at or above the PA-IC_{90} for a year following a single IM injection in rodents

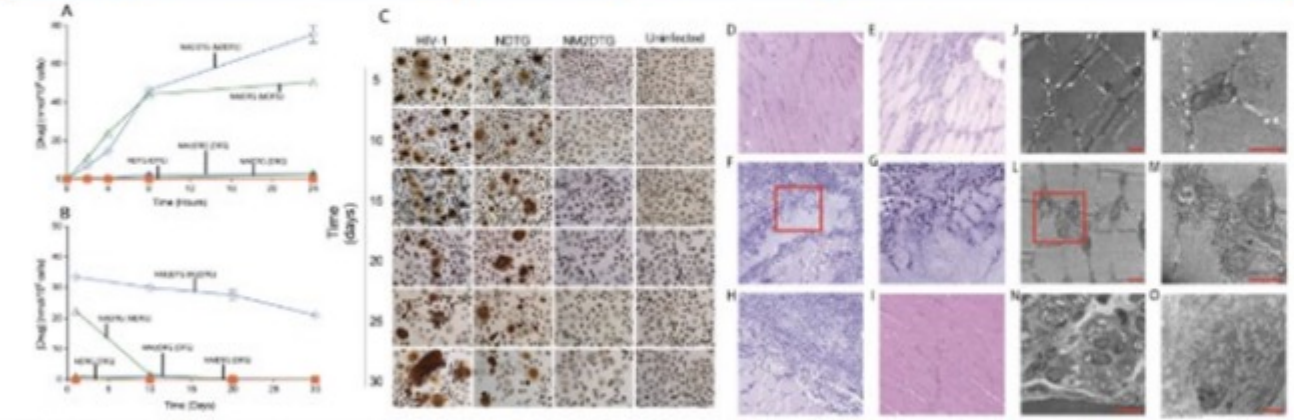
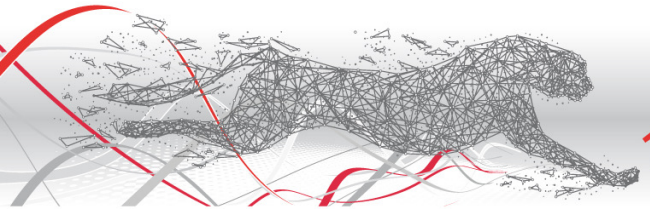


Fig. 2. Biological, histological and electron microscopic characterization of NM2DTG. **(A)** drug uptake and **(B)** retention in MDM measured over 24 h and 30 days, respectively, after treatment with prodrug nanoformulations at concentration of 25 μM. Results are expressed as the mean ± SEM for N = 3. **(C)** Antiretroviral responses were recorded after HIV-1_{ADA} challenge at a multiplicity of infection (MOI) of 0.1 infectious virions/cell at recorded times following treatment with either NDTG or NM2DTG at 1 μM concentrations for 8 h. HIV-1p24 antigen levels were assessed in fixed MDM by immunohistochemical staining. **(D-H)** H&E staining of caudal thigh muscle in histological sections after dissection from rats 3 days following IM injections. **(D)** Control (uninjected), **(E)** sham (saline-injected) control and **(F-H)** NM2DTG (45 mg DTG-eq./kg) treated muscle sections. **(I)** H&E staining of caudal thigh muscle in histological sections after dissection from rats 57 days following IM injection of NM2DTG at 45 mg DTG-eq./kg. Representative images for panel **(F)** at 10X magnification have been provided at 40X in panel **(G)**. **(J-O)** Replicate muscle samples were examined by transmission electron microscopy (TEM) from rats three days post-treatment. **(J-K)** uninjected and **(L-M)** Sham (saline-injected) controls show normal muscle histology. **(N)** Rats injected with NM2DTG show cell infiltration with ingestion of the nanoformulation into endosomal vesicles at day 3. Representative images for panel **(L)** at 10X magnification have been provided at 40X in panel **(M)**. **(O)** TEM of monkey muscle shows the nanoformulation depot in macrophages at day 364. Scale bars – 500 nm **(J-M)**, 10 μm **(N)**, 2 μm **(O)**.

CONCLUSIONS

- A single intramuscular injection of the NM2DTG prodrug nanocrystal generated DTG levels at or above the PA-IC_{90} for up to one year. These PK data sets were recorded in rodents and rhesus macaques.
- DTG prodrug depots in spleen, inguinal lymph node, liver and muscle tissues were 20, 400, 6,and 3800 μg/g at a year in rhesus.
- The extended NM2DTG PK profile is associated with prodrug nanocrystal tissue dissolution and pH.
- NM2DTG is readily was retained and provides protection beyond 30 days in macrophages challenged with HIV-1_{ADA}.

CROI 2022

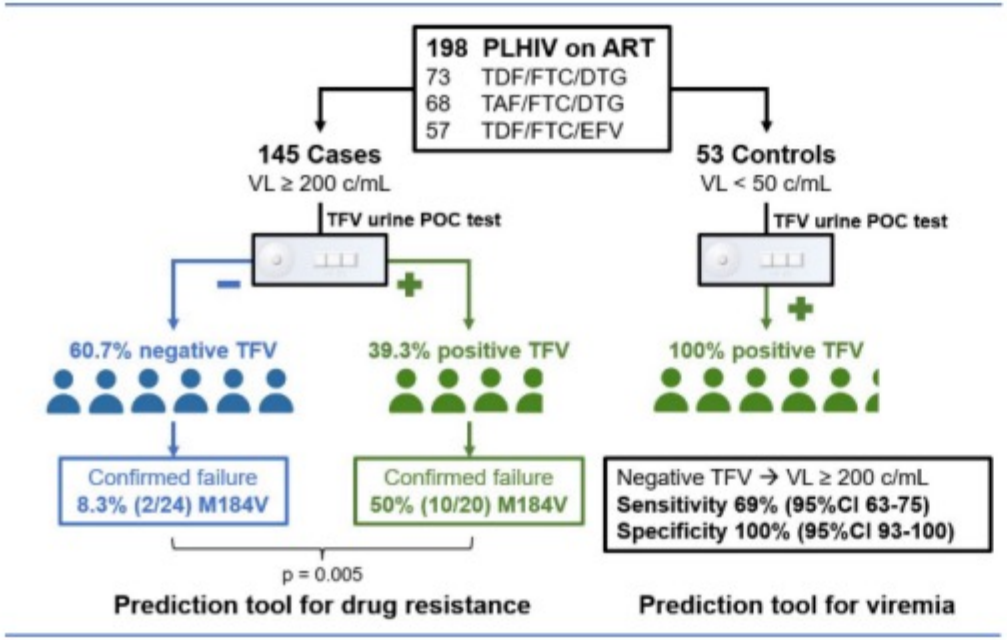


Tenofovir Urine Point-of-care Test Predicts Viremia and Drug Resistance During ART

451

Lucas E. Hermans[1,2,3], Chijioke N. Umunnakwe[4], Samanta T. Lalla-Edward[3], Shane Hebel[5], Willem D.F. Venter[3], Hugo A. Tempelman[4], Annemarie M.J. Wensing[2,3]

1: University of Cape Town, Cape Town, South Africa. 2: University Medical Center Utrecht, Utrecht, The Netherlands. 3: Ezintsha, University of the Witwatersrand, Johannesburg, South Africa. 4: Ndlovu Care Group, Groblersdal, South Africa. 5: OraSure Technologies Inc., Pennsylvania, USA.



RESULTS – PREDICTION OF VL ≥200 c/mL

Of 145 case participants with VL ≥200 c/mL, 39.3% had ≥1 positive urine-TFV test. Of 228 case samples, 30.7% were urine-TFV positive. 100% of controls were urine-TFV positive. Negative urine-TFV had a sensitivity of 69.3% [63-75] and specificity of 100% [93-100] for prediction of VL ≥200 c/mL.

All samples (n = 281)	VL ≥200 c/mL	VL <50 c/mL	
urine-TFV NEGATIVE	158 (69%)	0 (0%)	158
urine-TFV POSITIVE	70 (31%)	53 (100%)	123
	228 (100%)	53 (100%)	281

Sensitivity	69%	95% CI: 63 - 75
Specificity	100%	95% CI: 93 - 100
Positive predictive value	100%	95% CI: 98 - 100
Negative predictive value	43%	95% CI: 34 - 52

RESULTS – PREDICTION OF DRUG RESISTANCE

In participants with confirmed failure (n = 44), positive urine-TFV predicted the presence of the M184V mutation (OR 10.4 [1.8-114.4] p=0.005) with a sensitivity of 83% [52-98] and specificity of 69% [50-84].

CONCLUSIONS

- Negative urine-TFV was highly predictive of viremia during TDF-/TAF-based ART.
- Positive urine-TFV during viremia on TDF-/TAF-based ART test was associated with an increased risk of NRTI resistance.
- Point-of-care TFV urine detection may allow for rapid insight into adherence, suppression, and drug resistance during ART.

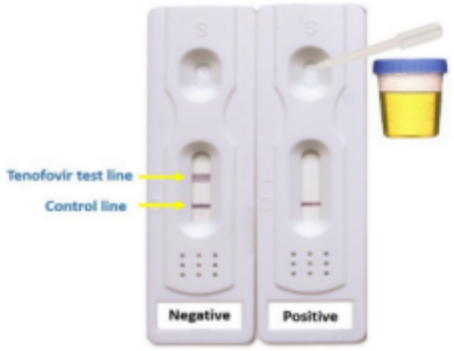
Point-of-Care Urine Tenofovir Testing to Detect HIV Drug Resistance

00515

Suzanne M. McCluskey[1,2,3], Katya Govender [4], John Adamson[4], Monica Gandhi[5], Matthew A. Spinelli[5], Mahomed Y. Moosa[6], Henry Sunpath[6], Pravi Moodley[6,7], Melendhran Pillay[7], Selvan Pillay[8], Winnie Muyindike[9], Godfrey Masette[9], Bethany Hedt-Gauthier[3,10], Vincent C. Marconi[11,12], Mark J. Siedner[1-4, 6,9]

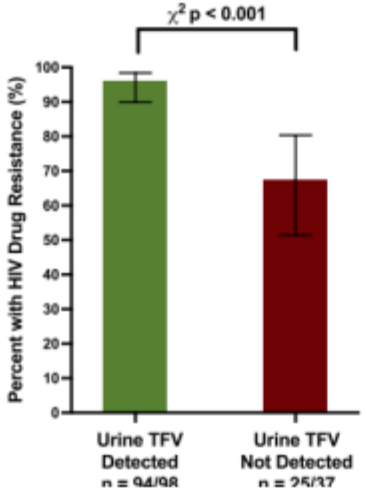
[1] Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA, USA, [2] Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA, [3] Harvard Medical School, Boston, MA, USA, [4] Africa Health Research Institute, Durban, South Africa, [5] Division of Infectious Diseases, University of California San Francisco, San Francisco, CA, USA, [6] University of KwaZulu-Natal, Durban, South Africa, [7] National Health Laboratory Service, Durban, South Africa, [8] Adrenergy Research Innovations, Durban, South Africa, [9] Mbarara University of Science and Technology, Mbarara, Uganda, [10] Harvard T.H. Chan School of Public Health, Boston, MA, USA, [11] Emory University School of Medicine, Atlanta, GA, USA, [12] Rollins School of Public Health, Emory University, Atlanta, GA, USA

Figure 1. Point-of-Care Urine Tenofovir Assay[2]



- Cutoff value for detection of TFV: 1,500 ng/mL
- Validated against liquid chromatography tandem mass spectrometry

Figure 2. Proportion with HIVDR in Participants with and without Detectable Urine TFV



In a setting with a high prevalence of HIV drug resistance, **the point of care urine tenofovir assay had a positive predictive value of 96% to detect HIV drug resistance.**

Expected Positive and Negative Predictive Values Across Varied Prevalence of HIVDR

Estimated HIVDR Prevalence	Positive Predictive Value	Negative Predictive Value
90%	97%	28%
75%	90%	54%
50%	76%	78%
25%	51%	91%
10%	26%	97%

Conclusions

- POC urine assay had a PPV of 96% to detect HIVDR in this population (observed HIVDR of 88%)
- The assay would also have a high NPV in settings where HIVDR prevalence is low (<10%)
- In both scenarios, the POC urine TFV assay could:
  - Provide a novel, low-cost method to confirm or exclude HIVDR
  - Inform clinical care and the need to switch to second-line ART
- Future work should assess its utility in real time

REPRIEVE
Randomized Trial to Prevent Vascular Events in HIV

Subclinical Atherosclerosis and Immune Activation Among US Females vs. Males With HIV

CROI Conference on Retroviruses and Opportunistic Infections

1423

Corresponding Author:
Markella V. Zanni, MD
mzanni@mgh.harvard.edu
Phone +1(617)724-6826

Markella V. Zanni[1*], Borek Foldyna[1*], Kenneth C. Williams[2], Tricia H. Burdo[3], Sara McCallum[1], Sara E. Looby[1], Patrick Autissier[2], Kathleen V. Fitch[1], Judith S. Currier[4], Michael T. Lu[1], Pamela S. Douglas[5], Heather J. Ribaudo[6], Steven K. Grinspoon[1] **for REPRIEVE Investigators**

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Boston College, Chestnut Hill, MA, USA, [3]Temple University, Philadelphia, PA, USA, [4]University of California Los Angeles, Los Angeles, CA, USA, [5]Duke Clinical Research Institute, Durham, NC, USA, [6]Harvard TH Chan School of Public Health, Boston, MA, USA. *Co-authors contributed equally

BACKGROUND

- Among people living with HIV (PWH), sex-differences in presentations of atherosclerotic cardiovascular disease (ASCVD) may be influenced by underlying differences in coronary artery plaque parameters, immune indices, or relationships therein.

METHODS

- REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV), a primary ASCVD prevention trial, enrolled anti-retroviral therapy (ART)-treated PWH globally.
- At study entry, a subset of US REPRIEVE participants underwent coronary computed tomography angiography (CCTA) and immune phenotyping (CCTA: **N=755**; CCTA + immune phenotyping: **N=725**).
- We characterized sex-differences in coronary artery plaque (log binomial regression for a relative prevalence rate [RR]) and immune indices (linear regression).
- Finally, we compared immune-plaque relationships by sex. Unless noted otherwise, analyses adjust for Pooled Cohort Equation ASCVD risk score.

RESULTS

Study Cohort

- The primary analysis cohort (N=755) included 631 (84%) males and 124 (16%) females (age 51±6 years).
- Median ASCVD risk was higher among males vs. females (4.9% [2.6–6.8] vs. 2.1% [0.9–3.7]).
- Obesity rates (BMI≥30 kg/m^2) were higher among females (48% vs. 21%).

Subclinical Atherosclerosis

- Prevalence of any coronary artery plaque and of plaques with either visible non-calcified portions and/or vulnerable plaque features (NC/V-P) was lower among females vs. males overall and controlling for ASCVD risk (**Figure 1**). **Any plaque:** RR=0.67; 95%CI: 0.50–0.92. **NC/V-P:** RR=0.71; 95%CI: 0.51–1.00) (both adjusted for ASCVD risk and BMI).
- Among those with any plaque, prevalence of NC/V-P did not differ by sex (*P=0.33*).

Females vs. males presented with:

1) Lower prevalence of coronary artery plaque
2) Lower prevalence of plaques with non-calcified portion and/or vulnerable plaque features (NC/V-P)
3) Key-differences of systemic immune activation parameters

Immune Activation Indices

- **Females vs. males** showed:
  - Higher levels of IL-6, hsCRP, and D-Dimer and lower levels of LpPLA-2 (*P<0.001* for all).
  - A lower percentage of total monocytes and a shift toward a higher percentage of inflammatory/intermediate (CD14+CD16+) and patrolling/non-classical (CD14-CD16+) vs. classical (CD14+CD16-) monocyte subsets (*P<0.001* for all).

Immune-Plaque Relationships (Figure 2)

Higher levels of LpPLA-2, MCP-1, and oxidized LDL were associated with higher coronary plaque (*P<0.02*) and NC/V-P prevalence, with no differences by sex (interaction *P>0.25*). Among females but not males, D-Dimer was associated with higher prevalence of NC/V-P (interaction *P=0.055*).

Figure 1: Prevalence of any coronary artery plaque or non-calcified plaque/ plaque with vulnerable features by ASCVD

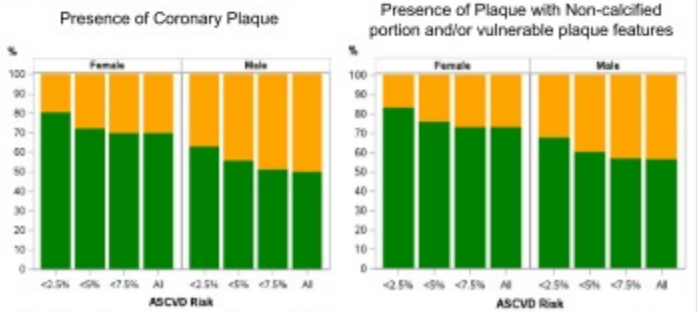
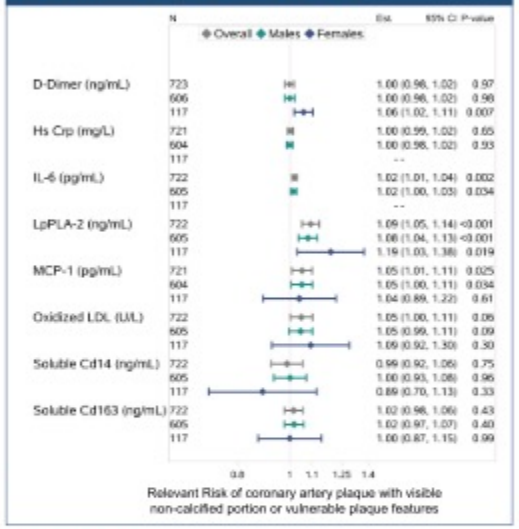


Figure 2: Relationships between systemic immune indices and plaque with visible non-calcified portions or vulnerable plaque features by sex



CONCLUSIONS

Females vs. males living with HIV had a lower prevalence of coronary artery plaque and plaque with visible non-calcified portions and/or vulnerable plaque features, as well as key differences in immune parameters. Immune-plaque relationships differed by sex for D-Dimer, but not other tested parameters. Understanding sex-specific immune drivers of subclinical coronary pathology will be key to tailoring ASCVD preventive therapies to PWH.

FUNDING Supported by NIH, NIH-LBI grants U01HL123336, to the REPRIEVE Clinical Coordinating Center, and U01HL123339, to the REPRIEVE Data Coordinating Center, and NIAID grant R01AI123001 (to MVZ and SEL), as well as funding from ViiV Healthcare, KOWA Pharmaceuticals and Gilead Sciences. NIAID has also supported this study through grants UM1 AI068636, which supports the ACTG Leadership and Operations Center, and UM1 AI106701, which supports the ACTG Laboratory.

577

HIV INFECTION AND INCIDENT ABDOMINAL AORTIC ANEURYSM AMONG 143,327 VETERANS

01811

Alexandra M. Filipkowski,[1] Suman Kunda, DSc, MSc,[2] Charles W. Alcorn, MA,[3] Joshua A. Beckman, MD, MSc,[2] Matthew S. Freiberg, MD, MSc,[2,4] Aaron W. Aday, MD, MSc[2]

1 - Fairfield University, Fairfield CT; 2 - Vanderbilt Translational and Clinical Cardiovascular Research Center, Division of Cardiovascular Medicine, Vanderbilt University Medical Center; 3 - University of Pittsburgh School of Public Health, Pittsburgh, PA; 4 - Veterans Affairs Tennessee Valley Healthcare System, Nashville, TN

American Heart Association.

BACKGROUND

- People with HIV (PWH) have an increased risk of cardiovascular disease (CVD).
- A recent European cohort study reported that PWH have a 4-fold higher prevalence of abdominal aortic aneurysm (AAA) than those uninfected.
- There are no studies reporting incident rates or risk of AAA among PWH compared to uninfected people
- We evaluated the association between HIV infection and incident AAA in a large cohort of U.S Veterans.

METHODS

Study Sample: Veterans Aging Cohort Study (VACS), a prospective, longitudinal, observational cohort of PWH and matched 1:2 with veterans living without HIV infection. We excluded participants with prevalent AAA. We followed veterans from their first clinical encounter on or after 4/1/2003 until an AAA event, death, or last date of follow-up through 7/31/2017.

Exposure: HIV status, HIV viral load, and CD4+ T cell count.

Outcome: AAA or AAA repair defined using ICD-9/10 or CPT codes.

Covariates: Age, race and ethnicity, sex, CVD risk factors, statin use, important comorbidities, HIV specific biomarkers and ART.

Analysis: We calculated descriptive statistics by HIV status (**Table 1**) and plotted cumulative incidence of AAA by HIV status and age groups (**Fig. 1**). We constructed Cox proportional hazards regression models to estimate the risk of incident AAA among PWH compared to those without HIV and time-updated HIV viral load and CD4 T cell count (**Fig 2**). Similar models restricted to PWH were constructed to determine which clinical characteristics and CVD risk factors were associated with incident AAA (**Fig 3**).

HIV Infection was *not* associated with an overall increased risk of AAA; however, there was an *increased* risk in AAA among HIV+ veterans who had elevated HIV viral load or low CD4 cell counts over time.

RESULTS

Table 1. Baseline Characteristics

	HIV Infected (n=44,092)	HIV Uninfected (99,235)
Age, mean (SD)	49.6 (10.7)	50.6 (10.5)
Male, N (%)	42,876 (97.2)	96,418 (97.2)
Race, N (%)		
White	17,558 (39.8)	39,758 (40.1)
Black	21,108 (47.9)	46,837 (47.2)
Hispanic	3,497 (7.9)	8,416 (8.5)
Other	1,929 (4.4)	4,224 (4.3)
Smoking status, N (%)		
Current	17,023 (38.6)	35,256 (35.5)
Former	5,066 (11.5)	13,431 (13.5)
Never	8,979 (20.4)	22,861 (23.0)
Diabetes, N (%)	5,054 (11.5)	19,057 (19.2)
Prevalent CVD, N (%)	5,653 (12.8)	17,018 (17.1)
HCV Infection, N (%)		
HCV negative	28,779 (65.3)	63,155 (63.6)
HCV positive viral load	9,726 (22.1)	10,335 (10.4)
HCV positive antibody only	2,938 (6.7)	3,241 (3.3)
Never tested/ unknown	2,612 (5.9)	22,432 (22.6)
Body mass index, mean (SD), kg/m2	25.9 (4.9)	29.6 (6.1)
Hypertension, N (%)	24,502 (55.6)	66,905 (67.4)
LDL cholesterol, median (Q1, Q3), mg/dL	101 (79, 126)	112 (89, 137)
HDL cholesterol, median (Q1, Q3), mg/dL	40 (32,50)	43 (36,52)
Triglycerides, median (Q1, Q3), mg/dL	137 (92, 216)	124 (83,191)
Statin therapy, N (%)	7,877 (17.9)	31,280 (31.5)
HIV Specific Variables		
CD4 Cell Count Variables, median (Q1, Q3), cells/mm3	386 (210, 593)	--
HIV-1 RNA, median (Q1,Q3), copies/mL	1,004 (75, 33,975)	--
ART Regimen, N (%)		
NRTI + PI	17,090 (38.8)	--
NRTI + NNRTI	17,008 (38.6)	--
NRTI + NNRTI + PI & other combinations	1,289 (2.9)	--
No ART	18,419 (41.8)	--

Figure 1. Cumulative Incidence of AAA by HIV and Age

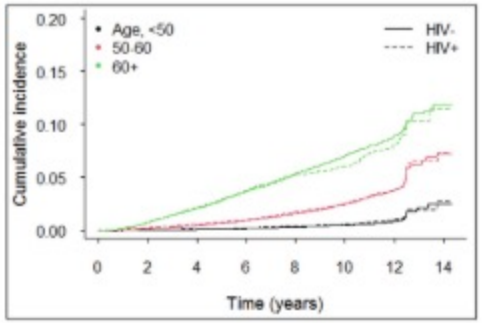
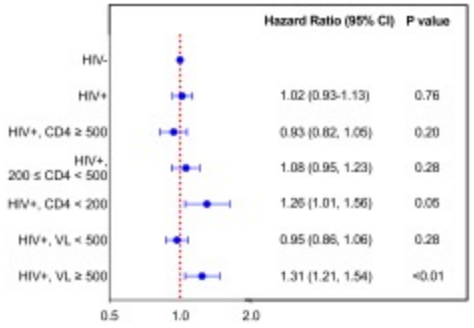
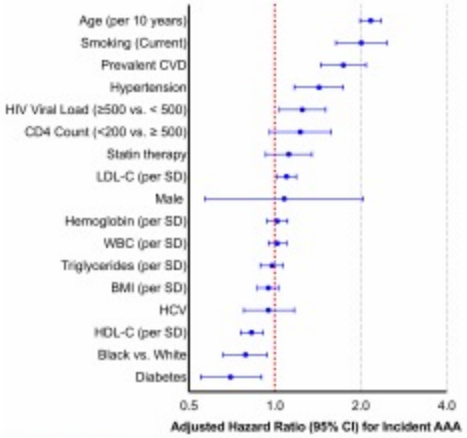


Figure 2. Risk of incident AAA by HIV status and time-updated HIV viral load and CD4 T cell count status



Models adjusted for age, sex, race, hypertension, diabetes, LDL-C, HDL-C, triglycerides, statin use, prevalent CVD, hepatitis C, smoking status, eGFR, hemoglobin, BMI, alcohol abuse. Missing values were imputed using multiple imputation. Stratification was performed using time-updated CD4 count and viral load.

Figure 3. Risk of Incident AAA by Clinical Characteristics and CVD risk factors Among Veterans with HIV



CONCLUSIONS

- HIV infection was not associated with an overall increased risk of AAA
- There was an increased risk in AAA among veterans with HIV who had elevated HIV viral load or low CD4 T cell counts over time
- Age, current smoking, history of CVD, hypertension and elevated HIV viral loads were most strongly associated with incident AAA among veterans with HIV

ADDITIONAL KEY INFORMATION

- **Limitations:** AAA outcome was not adjudicated, Majority of participants were male
- **Acknowledgments:** Thanks to the **American Heart Association, Drs Freiberg, Aday,** and **Barnett** for their mentorship as well as **VACS programmers and biostatisticians** for their programming assistance and statistical analyses. This work was funded by grants AHA SFVRN 882067, NIH K23 HL151871, NIH NIAAA U24-AA020794, U01-AA020790, U24-AA022001, U01-AA026224, U10 AA013566-completed and in kind by the US Department of Veterans Affairs
- **Contact Information:** alexandra.filipkowski@student.fairfield.edu

Atrial Fibrillation Risk Factors Among Patients in HIV Care in the United States

00587

Robin M. Nance[1], Joseph A.C. Delaney[2], James S. Floyd[1], Michael S. Saag[3], Richard D. Moore[4], Jeanne C. Keruly[4], Mari M. Kitahata[1], Bridget M. Whitney[1], W. Chris Mathews[5], Edward R. Cachay[5], Greer Burkholder[3], Amanda L. Willig[3], Sonia Napravnik[6], Heidi M. Crane[1], Susan R. Heckbert[1]

[1]University of Washington, Seattle, WA, US, [2]University of Manitoba, Winnipeg, CA, [3]University of Alabama, Birmingham, AL, US, [4]The Johns Hopkins University, Baltimore, MD, US, [5]University of California, San Diego, CA, US, [6]University of North Carolina, Chapel Hill, NC, US,

BACKGROUND

- People with HIV (PWH) are at increased risk of cardiovascular disease including atrial fibrillation (AF).
- Consequences of AF include an increased risk of heart failure and stroke.
- In PWH, therapeutic advances that reduce chronic inflammation, such as effective antiretroviral therapy (ART), may reduce AF risk.
- Relatively little is known about risk factors for AF among PWH.
- This study examined the association of traditional AF risk factors and HIV-related factors with incident AF.

METHODS

- Conducted at four sites in the United States in the Center for AIDS Research Integrated Network of Clinical Systems (CNICS) clinical care cohort.
- Incident AF from 2008-2017 was ascertained from clinical data and then adjudicated through physician review of medical records.
- Ten controls without AF were matched on site to each incident AF case using incidence density sampling

Table 1. Description of included participants

	Atrial fibrillation cases (n=97) % or Median (IQR)	Controls (n=970) % or Median (IQR)
Age, yrs	56 (51,61)	48 (41,54)
Men, %	90	78
Race/ethnicity, %		
White	54	39
Black	39	42
Hispanic	5	15
Other	2	4
HIV risk factor, %		
Men who have sex with men	47	48
Heterosexual	22	26
Intravenous drug use	28	23
Other	3	3
Treated hypertension, %	65	33
Diabetes, %	31	12
Current tobacco smoking, %	38	39
Coronary disease	32	7
Heart failure	22	3
Chronic obstructive pulmonary disease	18	7
Recent VL >400 copies/mL, %	23	16
Recent CD4, cells/mm^3	391 (269,632)	526 (336,752)
Antiretroviral therapy at index date, %		
Regimen with INSTI, NNRTI, or PI core	51	74
Regimen with 2 or more cores	33	14
Not on antiretroviral therapy	16	12

Atrial fibrillation risk factors known in the general population, lack of ART, and multi-core ART regimens were risk factors for incident AF in PWH.

- The index date was the AF diagnosis date for cases; for controls it was the date of the AF case with whom they were matched.
- Potential risk factors were ascertained from lab results, medication prescription records, diagnosis codes, and patient self-report at the closest available date to the index date.
- Associations of potential risk factors with incident AF were evaluated using multivariable conditional logistic regression

RESULTS

- 97 incident AF cases and 970 matched controls were included.
- Overall, the mean age was 48 years, 21% were female, and 87% were on ART, and cases had higher recent CD4 cell counts and higher HIV viral loads (Table 1).
- Traditional cardiovascular risk factors including older age, underlying coronary disease, heart failure, and chronic obstructive pulmonary disease were significantly associated with AF in multivariable conditional logistic regression models (Table 2).
- Both non-use of ART and a regimen with two or more core classes (integrase strand transfer inhibitor, non-nucleoside reverse transcriptase inhibitor, or protease inhibitor) were associated with higher odds of AF compared with a regimen with one core class (OR 2.86, 95% CI 1.39, 5.88 and OR 1.90, 95% CI 1.05, 3.41, respectively).
- In sensitivity analyses, adjustment for HIV viral load and CD4 count attenuated the ART regimen associations, and higher CD4 count was associated with a reduced risk of AF (OR per 100 higher CD4 count 0.91, 95% CI 0.84, 0.98).

Table 2. Multivariable conditional logistic regression analysis of risk factors for incident atrial fibrillation in CNICS (97 AF cases, 970 controls)

	Odds ratio	95% Confidence interval
Age, per 10 yrs	1.89	1.43, 2.49
Male sex	2.13	0.82, 5.54
Race/ethnicity		
White	Ref.	
Black	0.54	0.29, 1.00
Hispanic	0.33	0.13, 0.82
Other	0.64	0.16, 2.55
Treated hypertension	1.61	0.93, 2.79
Diabetes	1.56	0.89, 2.75
Current smoking	1.14	0.69, 1.87
Coronary disease	2.03	1.01, 4.06
Heart failure	3.96	1.84, 8.49
Chronic obstructive pulmonary disease	1.97	1.01, 3.83
Antiretroviral therapy at index date		
Regimen with INSTI, NNRTI, or PI core	Ref.	
Not on antiretroviral therapy	2.86	1.39, 5.88
Regimen with 2 or more cores	1.90	1.05, 3.41

CONCLUSIONS

- PWH were found to share many risk factors for AF that are known in the general population.
- HIV-specific factors of not using ART or using a multi-core ART regimen (which can indicate a longer duration of HIV or more ART treatment experience) were also associated with incident AF.
- Strengths of this study include the geographic, racial, and ethnic diversity of the participants, collection of data from the current ART era, careful adjudication of AF, and the availability of extensive clinical data.
- Limitations include the relatively small number of AF cases, lack of power to study specific ART regimens, and the possibility of residual confounding

AUTHOR CONTACT INFORMATION

- Robin M Nance, rmnance@uw.edu

CORONARY FLOW RESERVE ON DTG/ABC/3TC AT BASELINE AND AFTER SWITCH TO BIC/FTC/TAF

583

Daniel M Huck[1], Brittany Weber[1], Sean Parks[1], Sanjay Divakaran[1], Jenifer M Brown[1], Courtney Bibbo[1], Leanne Barrett[1], Jon Hainer[1], Camden Bay[2], Laurel Martell[1], Laura Kogelman[3], Virginia Triant[4], Jacqueline Chu[4], Nina Lin[5], Kathleen Melbourne[6], Paul E Sax[7], Marcelo Di Carli[1]

[1]Cardiovascular Imaging Program, Departments of Medicine and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA, [2]Departments of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA, [3]Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston MA, USA, [4]Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA, [5]CDivision of Infectious Diseases, Boston Medical Center, Boston MA, USA, [6]HIV Medical Affairs, Gilead Sciences, Foster City, CA, [7]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA

BACKGROUND

- *Do people with HIV have impairment in myocardial blood flow compared to matched people without HIV?*
- *Will switching from the abacavir-containing antiretroviral regimen DTG/ABC/3TC to BIC/FTC/TAF improve myocardial blood flow?*

HIV infection and abacavir-containing antiretroviral regimens associated with

- endothelial inflammation and dysfunction
- increased cardiovascular risk

Positron emission tomography (PET) derived coronary flow reserve (CFR): ratio of peak vasodilator stress to rest myocardial blood flow

- integrates the hemodynamic effects of focal stenosis, diffuse atherosclerosis and microvascular dysfunction
- higher CFR = better coronary vascular health
- powerful marker of cardiovascular risk.

METHODS

Prospective, single-arm, multi-center, open-label trial switching virologically suppressed people with HIV on DTG/ABC/3TC to BIC/FTC/TAF

- Cross-sectional comparison 1:3 matched non-HIV controls

HIV+
Men>45, Women >55
Stable with virologic suppression > 1 year
At least one coronary risk factor (current smoking, dyslipidemia, hypertension, diabetes, obesity, 10-year CV event risk >7.5%)

HIV- Controls
Referred for clinically indicated PET (most with symptoms)
Matching on sex/gender, age, race ethnicity, cardiovascular risk factors (hypertension, diabetes, smoking), coronary artery calcium score

HIV+ had vasodilator-stress and rest PET myocardial perfusion imaging at baseline, then switched to BIC/FTC/TAF for 24-week course prior to repeat PET.

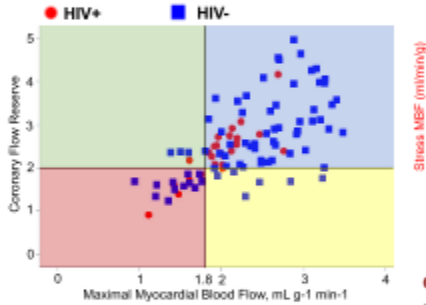
People with HIV (PWH) on DTG/ABC/3TC had statistically significantly **lower coronary flow reserve** (CFR) at baseline compared to **matched controls without HIV**. There was no significant change in CFR after switching to BIC/FTC/TAF overall; however, **those with an abnormal CFR at baseline** experienced an **increase after switch.**

RESULTS

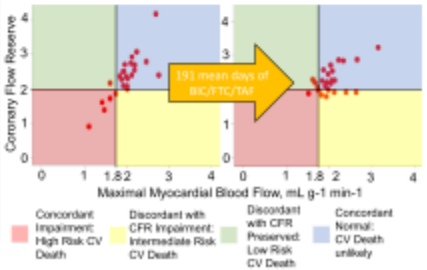
25 PWH were majority male (68%), cisgender (100%) and Black or Hispanic (56%) with mean age of 57 years. Controls were similar.

Characteristic, N (%) or mean ± SD	HIV+ (N=25)	HIV- (N=75)
Demographics		
Gender (cis male)	17 (68%)	51 (68%)
Age, years	57 ± 6	57 ± 6
Race/ethnicity		
Black Non-Hispanic	8 (32%)	24 (32%)
White Non-Hispanic	11 (44%)	37(49%)
White Hispanic	6 (24%)	14 (19%)
Metabolic Risk Factors		
Hypertension	16 (64%)	48 (64%)
Dyslipidemia	13 (52%)	38 (51%)
Diabetes	3 (12%)	10 (13%)
Family history of CAD	8 (33%)	24 (32%)
History of or current smoking	10 (40%)	31 (41%)
BMI, kg/m2	27.7 ± 4.7	33.7 ± 8.9
Coronary artery calcium (CAC)		
Absent	16 (64%)	48 (64%)
Mild or Moderate	7 (28%)	25 (34%)
Severe	2 (8%)	2 (3%)
ASCVD Risk, 10 year (%)	10.1 ± 6.2	10.7 ± 7.7
HIV-related Factors		
HIV Duration, years	20 ± 6	N/A
CD4 Count, cells/mm^3	734 ± 274	N/A
Stress-Test Related Factors		
Systolic Blood Pressure, mmHg	126 ± 23	143 ± 24
Diastolic Blood Pressure, mmHg	70 ± 10	78 ± 12
Heart Rate, beats/minute	62 ± 9	68 ± 11
Left Ventricle Ejection Fraction, %	56 ± 4	68 ± 11
Rest Rate Pressure Product (RPP)	8021 ± 2123	9753 ± 2508
Myocardial Blood Flow (MBF)		
Rest MBF, ml/min/g	0.68 ± 0.13	0.88 ± 0.21
Stress MBF, ml/min/g	1.97 ± 0.37	2.40 ± 0.63
CFR, corrected for rest RPP	2.34 ± 0.62	2.68 ± 0.91

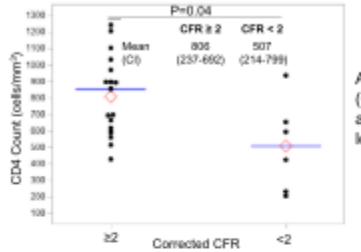
Mean CFR 2.34 (95% CI 2.08-2.60) in HIV+, lower than non-HIV matched patients of 2.68 (95% CI 2.47-2.89, p=0.03).
PWH maintained virologic suppression, with no adverse events



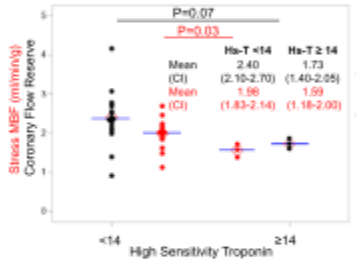
Mean CFR 2.29 (95% CI 2.13-2.45) after mean 6.3 months of BIC/FTC/TAF treatment, unchanged from baseline (p=0.61).



In exploratory analysis, among PWH with reduced CFR at baseline (<2.00, N=6), CFR increased significantly from 1.58 (95% CI 1.17-1.99) to 2.02 (95% CI 1.81-2.22, p=0.02).



Abnormal CFR (<2, N=6) associated with lower CD4 count



Elevated high sensitivity troponin (≥14, N=3) associated with lower CFR and stress myocardial blood flow (MBF)

CONCLUSIONS

- Virologically suppressed asymptomatic PWH on abacavir-containing regimen have subclinical coronary vasomotor dysfunction compared to matched non-HIV controls
- Although switching to BIC/FTC/TAF for 6 months did not improve CFR overall, PWH with low CFR at baseline did have improvement in CFR after switch
  - PWH with greater impairment in CFR on DTG/ABC/3TC may derive more benefit from switching to BIC/FTC/TAF
  - Lower CD4 count and elevated high sensitivity troponin may identify PWH who have low CFR
  - Further research needed to explore this subpopulation

ADDITIONAL KEY INFORMATION

Key Abbreviations:
DTG/ABC/3TC = dolutegravir/abacavir/lamivudine; BIC/FTC/TAF = bictegravir/tenofovir alafenamide/emtricitabine; CFR = coronary flow reserve; MBF = Myocardial blood flow; ASCVD = atherosclerotic cardiovascular disease; SD = standard deviation; ARV = antiretroviral

Disclosures: Funding for this study provided by Gilead Sciences, Inc.

Author Contact Information: Daniel Huck, Brigham and Women's Hospital,
Email: dhuck@bwh.Harvard.edu

CO-OCCURING OBESITY AND HIV ARE NOT ASSOCIATED WITH AN INCREASED ODDS OF DIABETES MELLITUS IN SOUTH AFRICA

Magodoro, IM[1, 2], Dungeni, MN[3], Castle, AC[4, 5, 7], Mureyani, S.[6], Siedner, MJ[4, 5, 7]

[1] University of Cape Town, Cape Town, South Africa; [2] EDGRC, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [3] Cavendish University Zambia, Lusaka, Zambia; [4] Africa Health Research Institute, KwaZulu-Natal, South Africa; [5] Massachusetts General Hospital, Boston, Massachusetts, USA; [6] Gweru District Hospital, Gweru, Zimbabwe; [7] Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

expert workshop HIV REAL TIME 10 ANNI
Post-CROI 2022

Background

- Obesity and antiretroviral therapy (ART)-treated HIV infection have been associated with increased insulin resistance, disordered beta-cell function and adipose tissue inflammation [1, 2].
- Co-morbid obesity increases the risk of diabetes mellitus (DM) among persons living with HIV (PWH) in high-income countries (HICs).
- Although both HIV and obesity are highly prevalent in much of sub-Saharan Africa, this relationship is less well established in low- and middle-income countries [3].

Objective

To determine whether **obesity among adult PLWH in South Africa is associated with increased DM occurrence**.

Methods

- Analysis of data among adults (≥20 years) with biomarker phenotyping data in the South Africa Demographic Survey (DHS) 2016, a nationally representative cross-sectional survey,.
- **Primary outcomes:**
  1) glycated hemoglobin (HbA1c) as a continuous measure
  2) prevalent diabetes mellitus (DM) defined as HbA1c >6.5%.
- **Primary exposures of interest:**
  1) HIV-serostatus
  2) Body mass index (BMI)
- Estimated associations between prevalent DM, HbA1c and BMI (continuous and categorical) stratified by HIV status were assessed by regression models and postestimation margins.
- Models adjusted for age, sex, race, smoking status, and urban/rural residence and use of inverse probability sampling weights to make population-level estimates.

Conclusions

People living with HIV in South Africa had significantly lower mean hemoglobin A1c and lower prevalence of DM across a broad range of body mass index.

Regional differences in health behavior, healthcare access and genetics should be further explored to elucidate mechanisms of metabolic disease among people with HIV.

Results

Table 1. Characteristics of the weighted sample.

Characteristic*	HIV-	HIV+
Number (%)	4,383 (78.9%)	1,171 (21.1%)
Male sex	2,060 (47.0%)	2,322 (31.8%)
Age (years)	43.7 (0.40	39.3 (0.5)
Urban residence	1,381 (68.5%)	367 (68.6%)
BMI (kg/m^2)	27.6 (0.1)	27.3 (0.3)
Prevalent DM	998 (22.9%)	219 (18.8%)
Median HbA1c (%)	6.1 (5.9, 6.4)	6.1 (5.9, 6.4)
Current smoker	1,025 (23.4%)	234 (20.0%)
Prevalent hypertension	1,834 (42.7%)	411 (36.1%)

Fig. 1 (a) Crude and (b) adjusted DM prevalence among adult (≥20 years old) South Africans by HIV status.

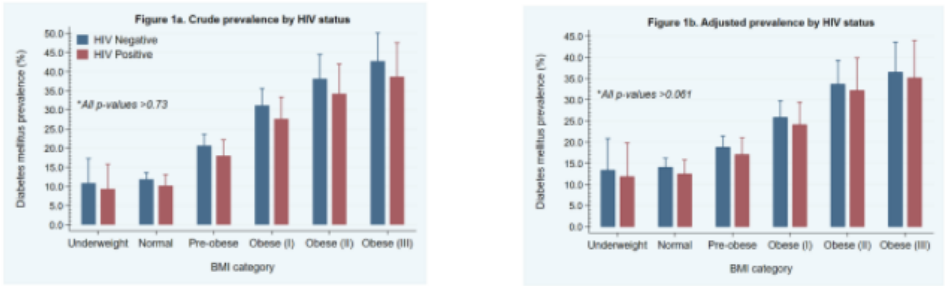
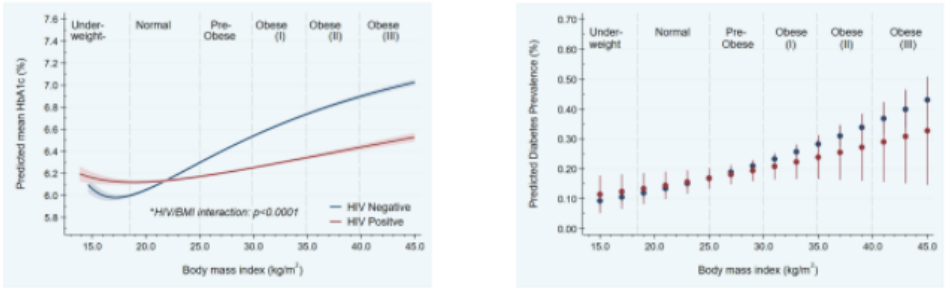


Fig 2. Predicted (a) mean HbA1c and (b) DM prevalence among adult (≥20 years old) South Africans by HIV status.



*Correspondence
Dr. IM. Magodoro:
Itai.Magodoro@uct.ac.za

Acknowledgements
Authors would like to thank Dr. Tom Pullum, PhD., and Dr. Mahmoud Elkasabi, PhD, at The DHS Program, ICF International, for their ongoing support.

References

1. Noubissi, E.C., Katte, J.C. and Sobngwi, E., 2018. Diabetes and HIV. Current diabetes reports, 18(11), pp.1-8.
2. Kalra, S., Kalra, B., Agrawal, N. and Unnikrishnan, A.G., 2011. Understanding diabetes in patients with HIV/AIDS. Diabetology & metabolic syndrome, 3(1), pp.1-7.
3. Dalal, S., Beunza, J.J., Volmink, J., Adebamowo, C., Bajunirwe, F., Njelekela, M., Mozaffarian, D., Fawzi, W., Willett, W., Adami, H.O. and Holmes, M.D., 2011. Non-communicable diseases in sub-Saharan Africa: what we know now. International journal of epidemiology, 40(4), pp.885-901.

AGE AND OBESITY AS RISK FACTORS FOR DIABETES IN AFRICANS WITH HIV

00604

Lisa Hamzah[1], Amelia Oliveira[2], Claire Norcross[2], Zoe Ottaway[2], Julie Fox[3], Fiona Burns[4], Andrew Ustianowski[5], Sarah Pett[4,6], Sarah Schoeman[7], Amanda Clarke[8], Caroline Sabin[4], Louise Goff[3], Frank Post[2,3], Cheryl Winkler[9], for the GEN-AFRICA study group.

[1]St George's University Hospitals NHS Foundation Trust, London, United Kingdom, [2]King's College Hospital NHS Foundation Trust, London, United Kingdom, [3]King's College London, London, United Kingdom, [4]University College London, London, United Kingdom, [5]University of Manchester, Manchester, England, [6]Central and NorthWest London NHS Foundation Trust, [7]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]University Hospitals Sussex NHS Foundation Trust, Brighton, United Kingdom, [9]National Cancer Institute, Frederick, MD, United States

BACKGROUND

- Diabetes is an important comorbidity in ageing populations.
- Age, male sex and obesity are risk factor for diabetes.
- We evaluated whether age, sex and obesity are independent risk factors for diabetes mellitus in people of African ancestry living with HIV in the UK.

METHODS

GEN-AFRICA study design

- Cross-sectional study of participants in the GEN-AFRICA study, a cohort individuals of African ancestry aged >18 years receiving routine HIV care in 15 clinics across the United Kingdom; participants were enrolled between 05/2018 and 02/2020, provided height and weight measurements, and completed questionnaires on comorbidities and medications. Kidney function (estimated glomerular filtration rate [GFR], proteinuria [urine protein/creatinine ratio, uPCR], and glycosuria) was assessed.
- The study included participants of sub-Saharan African ancestry. Participants of Caribbean or mixed ancestry (n=559) were excluded, as were those without height/weight measurements (n=40), diabetes status (n=21), or end-stage kidney disease (n=87). Individuals with low BMI (<18.5 kg/m^2), n=12) were also excluded.

Exposures, outcomes and covariates

Exposures of interest	• Age, sex, obesity (BMI >30 kg/m^2)
Primary Outcome	• Diabetes mellitus (self-reported; corroborated through review of medical records)

Covariates

Demographics	Age, gender, sexual orientation
HIV measures	Prior AIDS, time since HIV diagnosis, use of ART, nadir/current CD4, HIV viral load
Co-infections	Hepatitis B surface antigen +, hepatitis C antibody +
Co-morbidities	Obesity, hypertension (self-reported), renal impairment (eGFR 15-60 mL/min/1.73m^2, proteinuria (uPCR >15 mg/mmol)

Statistical analysis:

- Associations between covariates were evaluated using logistic regression; variables with p<0.1 in univariable analysis were included in multivariable models.
- Models were a priori stratified by sex.
- Smoking status, HIV transmission risk and cardiovascular disease were not included due to low numbers, collinearity and likely reverse-causality respectively.

RESULTS

- 218/2308 (9.4%) were diagnosed with diabetes (99% Type 2)
- They were more likely to be male, older, obese, with lower nadir CD4 cell count, hypertension, renal impairment and proteinuria

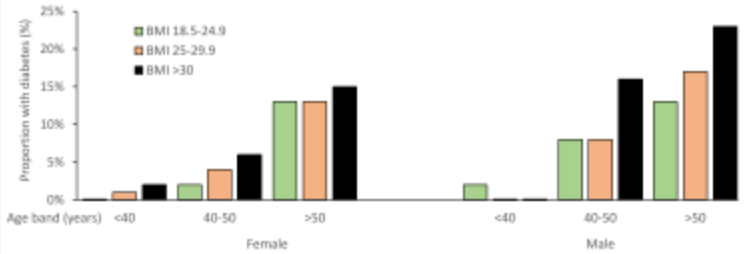
Table 1: Baseline characteristics

		Overall N=2,308	No diabetes N=2,090	Diabetes N=218	P value
Demographics	Male (vs. female)	866 (37.5%)	755 (36.1%)	111 (50.9%)	<0.001
	Age in years				<0.001
	<40	423 (18.3%)	419 (20.0%)	4 (1.8%)	
	40-50	905 (39.2%)	847 (40.5%)	58 (26.6%)	
	>50	980 (42.5%)	824 (39.4%)	156 (71.6%)	
	HIV risk factor (heterosexual)	2,012 (87.2%)	1,821 (87.1%)	191 (87.6%)	0.14
	Region of ancestry				0.82
	South Africa	554 (24.0%)	497 (23.8%)	57 (26.1%)	
	East Africa	770 (33.4%)	696 (33.3%)	74 (33.9%)	
	Central Africa	156 (6.8%)	142 (6.8%)	14 (6.4%)	
	West Africa	828 (35.9%)	755 (36.1%)	73 (33.5%)	
HIV-parameters	Years HIV diagnosis	14.1 [6.3]	14.0 [6.2]	14.8 [6.8]	0.088
	Currently on ART	2,285 (99.0%)	2,070 (99.0%)	215 (98.6%)	0.55
	Previous AIDS	566 (25.1%)	501 (24.5%)	65 (30.7%)	0.13
	Nadir CD4 cell count	198 [81-333]	200 [84-333]	173 [41-324]	0.019
	Current CD4 cell count	556 (409-721)	555 (409-718)	563 (403-778)	0.29
	HIV VL >200 cps/ml	150 (6.5%)	133 (6.4%)	17 (7.8%)	0.41
	Hepatitis B	139 (6.1%)	119 (5.8%)	20 (9.3%)	0.037
	Hepatitis C	24 (1.1%)	22 (1.1%)	2 (0.9%)	0.84
Comorbidities	BMI kg/m^2				0.031
	18.5-25	472 (20.5%)	442 (21.1%)	30 (13.8%)	
	25-30	821 (35.6%)	748 (35.8%)	73 (33.5%)	
	30-35	618 (26.8%)	552 (26.4%)	66 (30.3%)	
	35-40	258 (11.2%)	227 (10.9%)	31 (14.2%)	
	>40	139 (6.0%)	121 (5.8%)	18 (8.3%)	
	Hypertension	722 (31.3%)	584 (28.0%)	138 (63.3%)	<0.001
	Diabetes				
	Cardiovascular disease	90 (3.9%)	77 (3.7%)	13 (6.0%)	0.098
	Smoking status (never)	1,915 (83.0%)	1,726 (82.6%)	189 (86.7%)	0.010
	Renal impairment	96 (4.2%)	71 (3.4%)	25 (11.5%)	<0.001
	Proteinuria	485 (21.9%)	403 (20.1%)	82 (38.5%)	<0.001

MSM = men who have sex with men; ART = antiretroviral therapy; AIDS = acquired immunodeficiency syndrome; hepatitis B = HBV surface antigen positive; hepatitis C = anti-hepatitis C (gp) antibody positive; BMI = body mass index; renal impairment = eGFR <60 mL/min/1.73m^2; proteinuria = uPCR >15 mg/mmol.

PREVALENCE OF DIABETES

- Obesity was more prevalent in females: 52 vs. 31%, p<0.001
- Diabetes was more prevalent in males: 12.8 vs. 7.4% p<0.001
- The prevalence of obesity and diabetes increased with age in both sexes (p<0.001)



FACTORS ASSOCIATED WITH DIABETES

Table 2: Univariate and multivariate associations with diabetes, stratified by sex

Exposure	FEMALE Univariate OR [95% CI]	P value	FEMALE Multivariate* OR [95% CI]	P value	MALE Univariate OR [95% CI]	P value	MALE Multivariate* OR [95% CI]	P value
Obesity	1.59 [1.05, 2.39]	0.02	1.19 [0.76, 1.85]	0.44	1.91 [1.27, 2.29]	0.002	1.40 [0.89, 2.20]	0.14
Age in years								
<40	1	0.0001	1	0.001	1	<0.001	1	0.01
40-50	4.56 [1.37, 15.2]		3.44 [0.99, 11.9]		12.3 [2.00, 117.0]		10.4 [1.38, 78.2]	
>50	15.6 [4.76, 51.5]		8.18 [2.30, 29.2]		29.5 [3.87, 224.4]		16.5 [2.24, 121.0]	
Current CD4 cell count	1.40 [1.00, 1.95]	0.05	1.52 [0.84, 2.77]	0.17	0.98 [0.71, 1.36]	0.93		
Hepatitis B	1.61 [0.75, 2.97]	0.75			1.69 [0.92, 3.09]	0.08	1.80 [0.94, 3.48]	0.08
Hypertension	4.57 [3.01, 6.92]	<0.001	2.49 [1.57, 3.95]	<0.001	3.97 [2.57, 6.11]	<0.001	2.26 [1.41, 3.60]	0.001
Renal impairment	5.29 [2.68, 10.4]	<0.001	2.46 [1.21, 4.99]	0.012	2.35 [1.18, 4.68]	0.01	0.75 [0.35, 1.63]	0.48
Proteinuria	1.60 [1.03, 2.48]	0.034	1.18 [0.73, 1.90]	0.50	3.84 [2.49, 5.91]	<0.001	3.02 [1.88, 4.76]	<0.001

*Adjusted for obesity, age, years HIV diagnosis, current CD4 cell count, hypertension, renal impairment and proteinuria

DISCUSSION

- Although obesity was more prevalent in African women, diabetes was more prevalent in African men. While both obesity and age (and hypertension, renal impairment, and proteinuria) were associated with diabetes in both female and males in univariable analyses, age remained significantly associated with diabetes, particularly amongst men, whereas obesity was no longer a significant risk factor in the adjusted analyses. Older African people with HIV should be regularly screened for diabetes.
- The limitations of this study include the cross-sectional nature of study (which precluded incorporation of the effects of antiretroviral medications), and the use of BMI (rather than measures of central obesity) to evaluate the relationship between obesity and diabetes mellitus.

CONCLUSIONS

- **Age was the strongest risk factor for diabetes** in this cohort of African people with well controlled HIV.
- Measures of central adiposity may be more useful predictors of diabetes, especially in African women with HIV.

The authors are grateful to the study participants. The GEN-AFRICA study received support from the Medical Research Council (UK) (through the KHP R&D Challenge Fund and the NIHR clinical research network

CROI 2022

UNIVERSITY OF ALBERTA | McGill UNIVERSITY | UNIVERSITÀ DEGLI STUDI DI BRESCIA | UNIBS | UNIMORE UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Poster No. 521

From NAFLD to MAFLD: implications of change in terminology in PWH

Giovanni Guaraldi

Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia, Modena, Italy

Disclosure: GG received research grant and speaker honorarium from Gilead, ViiV, MERCK and Jansen. GG attended advisory boards of Gilead, ViiV and MERCK.

Background

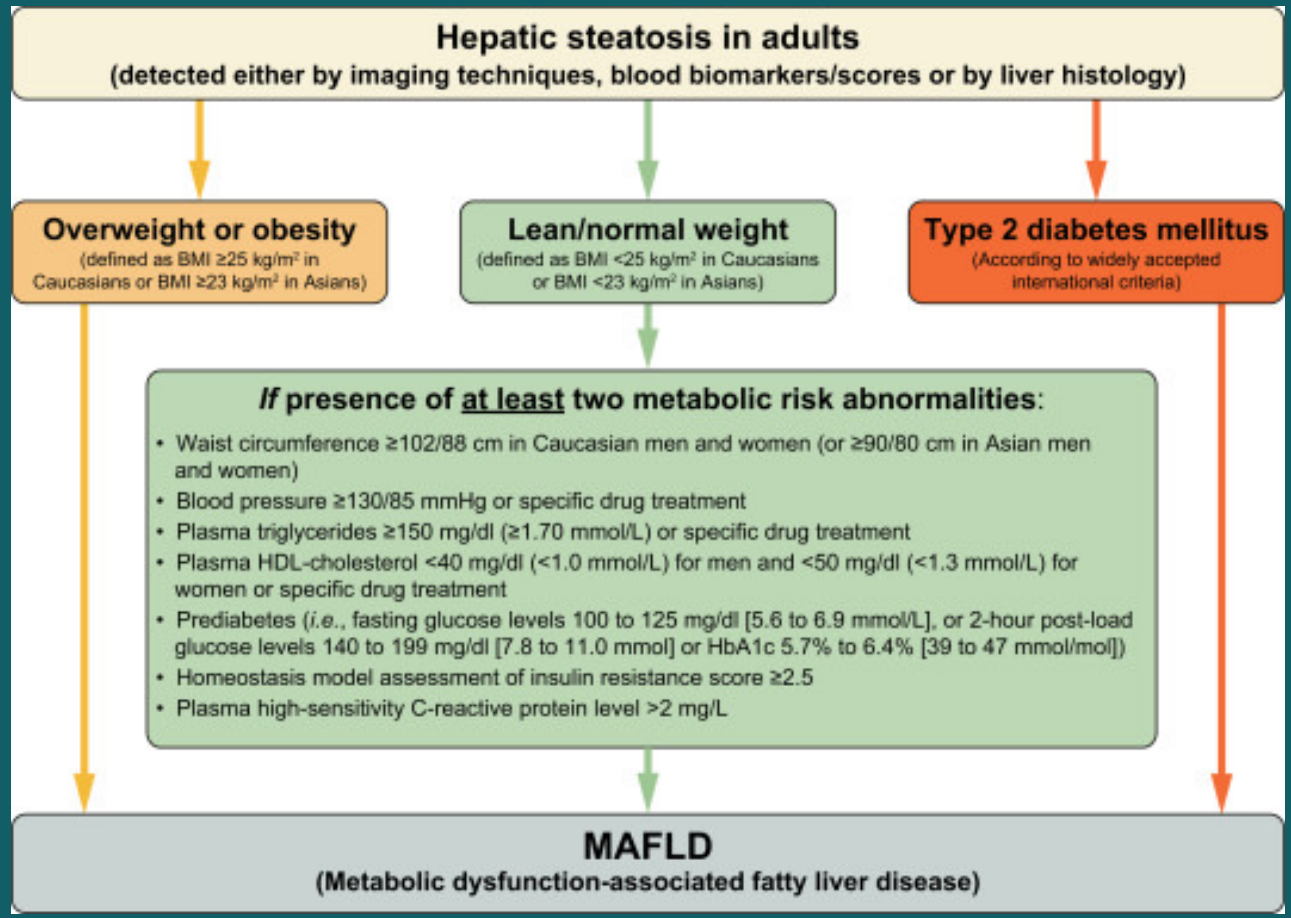
- Metabolic associated fatty liver disease (MAFLD) has been recently proposed as a new concept to describe non-alcoholic fatty liver disease (NAFLD), based on positive diagnostic criteria rather than exclusionary ones.

- The ongoing debate regarding NAFLD/MAFLD construct has not yet reached HIV arena.

- **Our objective** was to characterize MAFLD in comparison to NAFLD and to determine prevalence and predictors of both conditions in people with HIV (PWH).

Methods

- A cross-sectional study of two prospective cohorts (Modena HIV Metabolic Clinic and LIVEHIV Montreal) comprising PWH that were screened for fatty liver disease (FLD).
- FLD was defined as controlled attenuation parameter of ≥248 dB/m.
- NAFLD was defined as FLD in absence of significant alcohol intake and HBV or HCV co-infection.
- Significant liver fibrosis was defined as liver stiffness ≥7.1 kPa.



- MAFLD was defined as the presence of FLD and at least one of the criteria shown in the Figure.

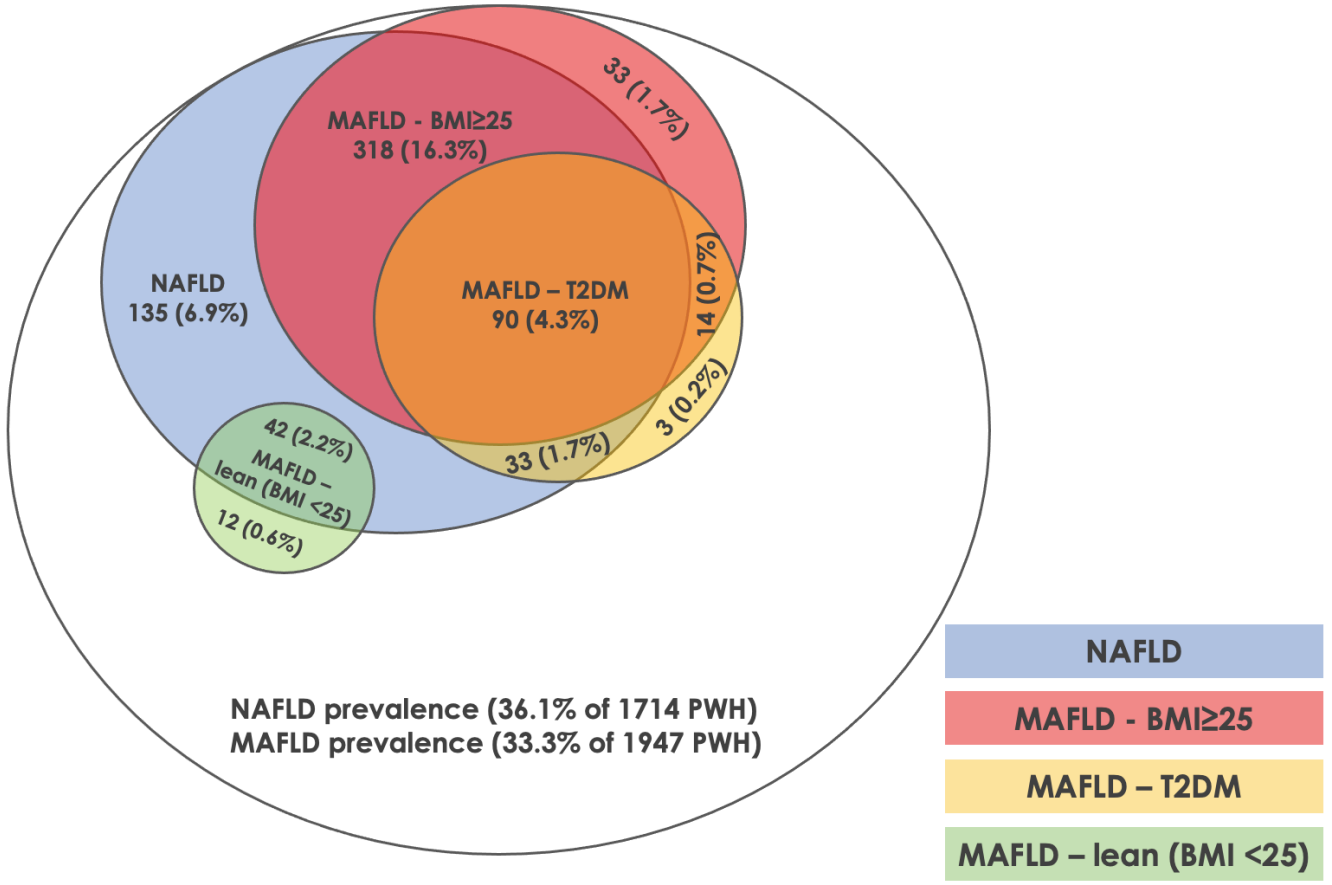
Results

- We included 1947 PWH. Mean age 54 years, 74% males, median HIV duration 21 years, median current CD4 703, 98% with undetectable HIV viral load.

- Prevalence of overweight and diabetes was 23.4% and 49.5%.

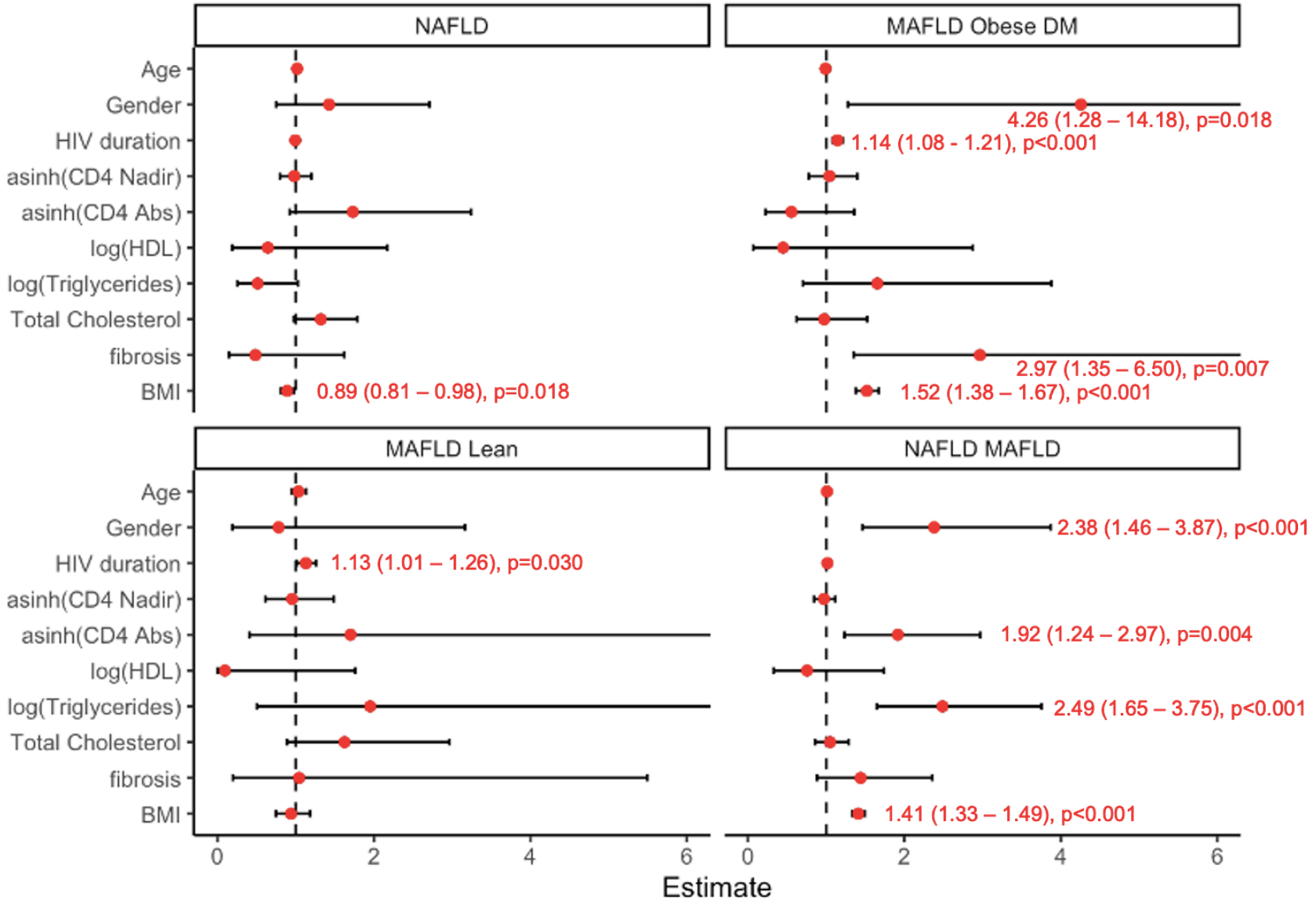
- NAFLD was diagnosed in 618/1714 (36.1%) PWH, after excluding PWH with significant alcohol intake (1.8%), HBV (1.2%), HCV (9.2%).

- MAFLD was diagnosed in 648 (33.3%) PWH.



Proportions of PWH with NAFLD, MAFLD and NAFLD/MAFLD overlap.

Results



- Liver fibrosis was associated with MAFLD with diabetes or BMI>25 kg/m^2.
- Longer time since HIV diagnosis was associated with lean MAFLD and MAFLD with BMI >25 kg/m^2.
- Male sex, higher CD4 cell count and triglycerides were associated with NAFLD/MAFLD overlap.

Conclusions

- PWH displayed a substantial overlap between NAFLD and MAFLD, but those with MAFLD and diabetes or overweight/obesity had higher risk of significant liver fibrosis.

- Both HIV-related and metabolic variables were independent predictors of NAFLD/MAFLD.

- Change of terminology may help to prioritize PWH requiring surveillance and interventions for the management of FLD and associated liver fibrosis.

CROI 2022

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia

UNIVERSITY OF ALBERTA · McGill UNIVERSITY · UNIVERSITÀ DEGLI STUDI DI BRESCIA · UNIBS · UNIMORE UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Poster No. 522

The pathway of NAFLD vs MAFLD toward significant fibrosis

Jovana Milic, MD, PhD

Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia, Modena, Italy

Disclosure: JM has nothing to disclose.

Background

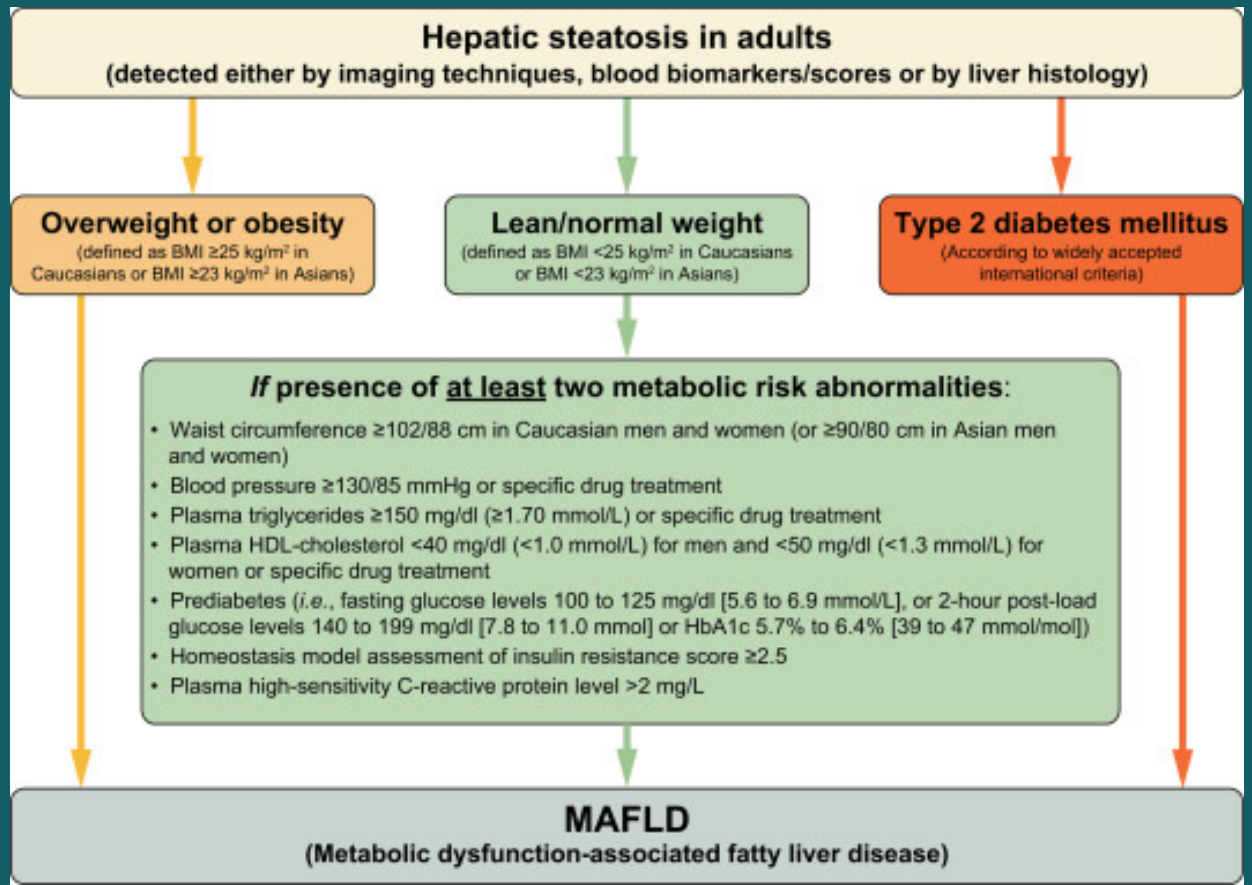
- Metabolic associated fatty liver disease (MAFLD) has been recently proposed as a new concept to describe non-alcoholic fatty liver disease (NAFLD), based on positive diagnostic criteria rather than exclusionary ones.

- The ongoing debate regarding NAFLD and MAFLD should consider risk of progression of fatty liver disease (FLD).

- We aimed to describe transition of NAFLD and MAFLD states towards significant fibrosis in people with HIV (PWH).

Methods

- A longitudinal study of two prospective cohorts (Modena HIV Metabolic Clinic and LIVEHIV Montreal) of PWH.
- FLD was assessed **at least twice** with controlled attenuation parameter (CAP ≥248 dB/m) by transient elastography
- Significant liver fibrosis was defined as liver stiffness ≥7.1 kPa.



Statistical analysis

- A continuous-time multi-state Markov model was used.
- The probabilities to switch from one state to another were modelled according to an exponential distribution for time-to-event data, considering censored follow-up times.
- The events were the transitions between the states.

Results

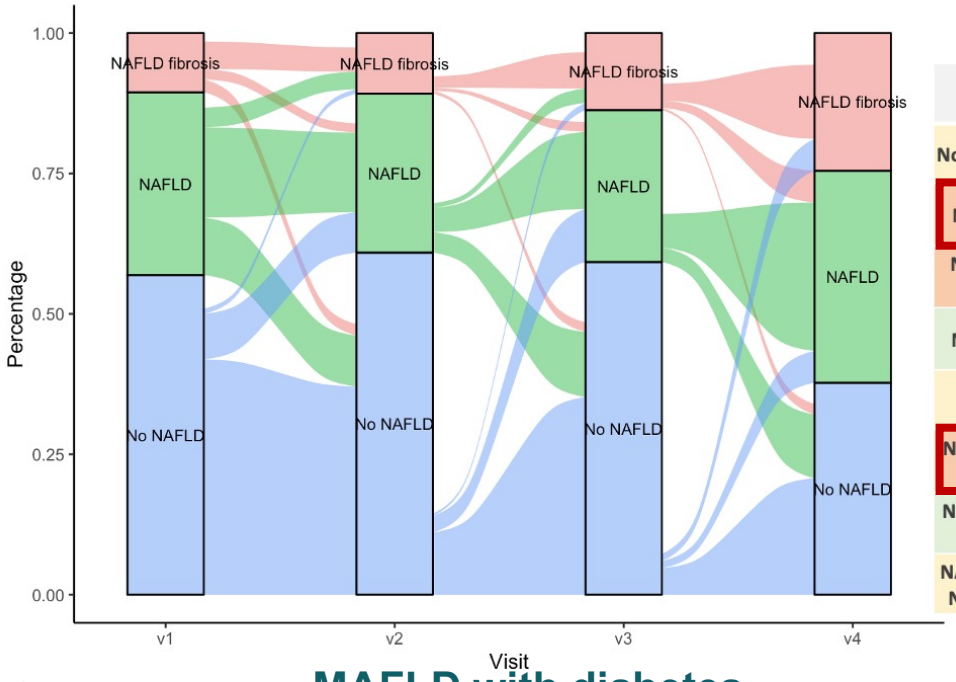
- A total of 888 PWH were screened for FLD, with a mean follow-up of 2 years, mean age 54.4 years, 77% males.

- At the first visit, after excluding PWH with alcohol intake and viral co-infections, prevalence of NAFLD was 42.9% (285/664).

- The overall prevalence of the MAFLD was 34.3% (305/888):
  - MAFLD with BMI≥25 kg/m^2 was present in 244 (27.5%),
  - MAFLD with diabetes in 86 (9.7%)
  - lean MAFLD in 33 (3.7%).

A

NAFLD

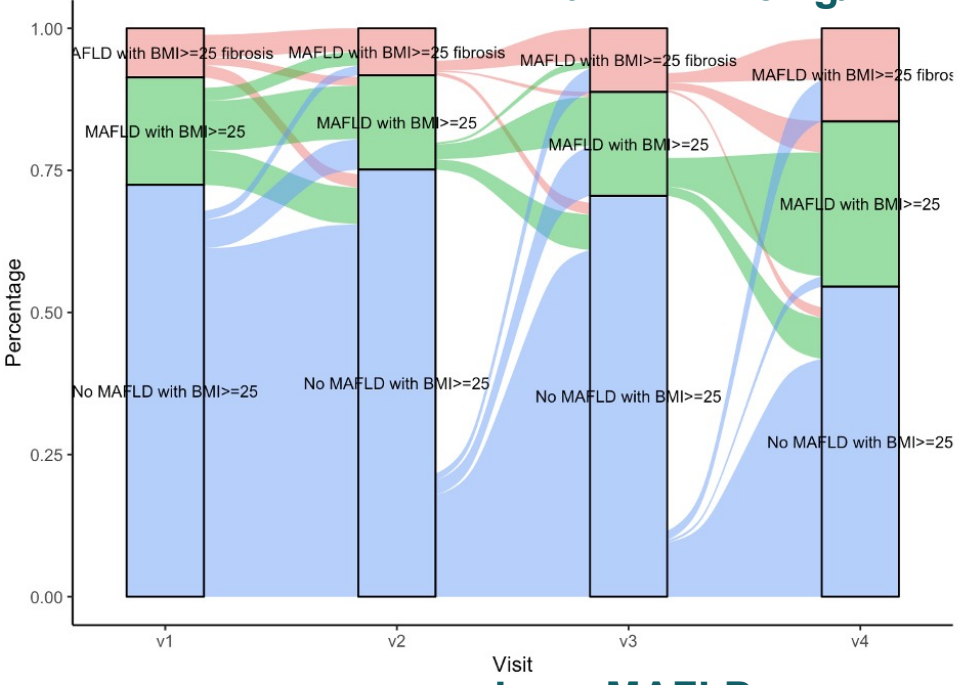


Probability of state transition for NAFLD

Path	Estimates
No NAFLD - No NAFLD	80.3%
No NAFLD - NAFLD	17%
No NAFLD – NAFLD with fibrosis	2.6%
NAFLD – no NAFLD	36.4%
NAFLD - NAFLD	53.4%
NAFLD – NAFLD with fibrosis	10.2%
NAFLD with fibrosis - NAFLD	21.3%
NAFLD with fibrosis – NAFLD with fibrosis	58.5%

B

MAFLD with BMI >25 kg/m^2

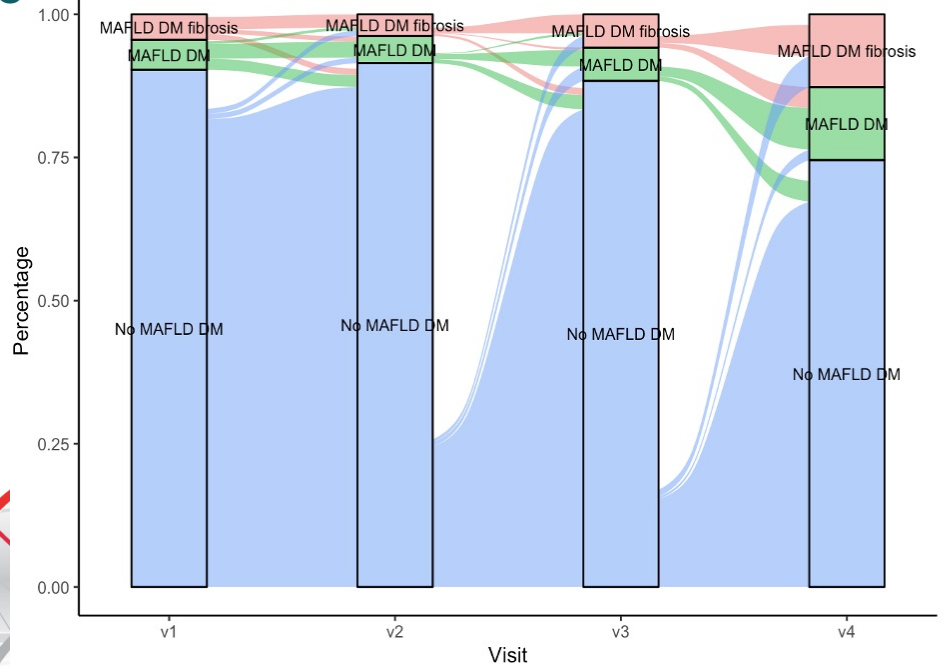


Probability of state transition of MAFLD with BMI ≥ 25

Path	Estimates
No MAFLD - No MAFLD	88.3%
No MAFLD - MAFLD	8.2%
No MAFLD – MAFLD with fibrosis	3.5%
MAFLD – no MAFLD	35.7%
MAFLD - MAFLD	53.1%
MAFLD – MAFLD with fibrosis	10.5%
MAFLD with fibrosis - MAFLD	18.8%
MAFLD with fibrosis – MAFLD with fibrosis	55.2%

C

MAFLD with diabetes

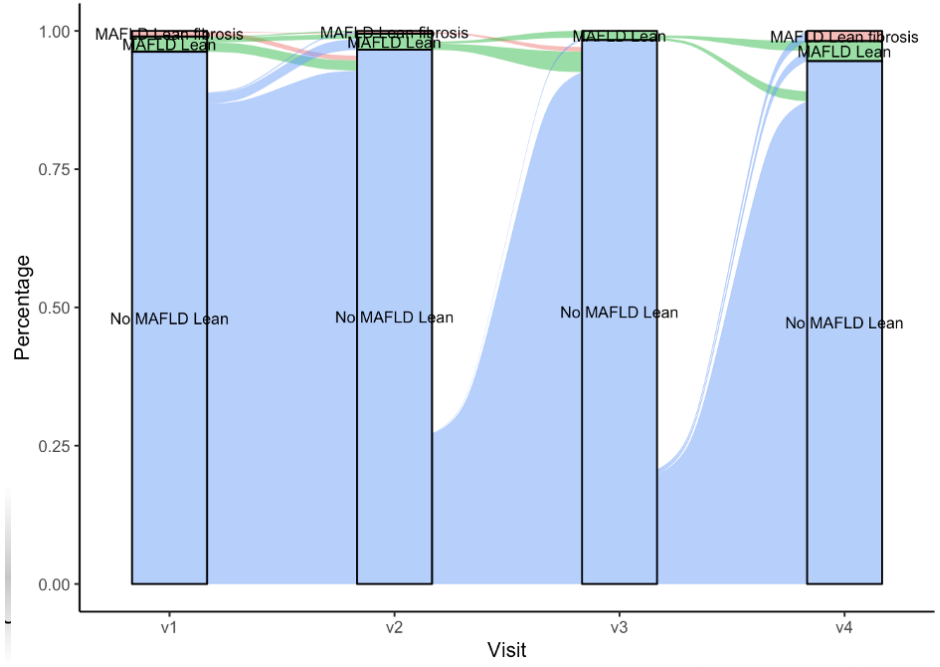


Probability of state transition of MAFLD with diabetes

Path	Estimates
No MAFLD - No MAFLD	96.9%
No MAFLD - MAFLD	1.5%
No MAFLD – MAFLD with fibrosis	1.6%
MAFLD – no MAFLD	40%
MAFLD - MAFLD	52.3%
MAFLD – MAFLD with fibrosis	7.7%
MAFLD with fibrosis - MAFLD	18.9%
MAFLD with fibrosis – MAFLD with fibrosis	58.5%

D

Lean MAFLD



Probability of state transition of MAFLD with BMI <25 (lean)

Path	Estimates
No MAFLD - No MAFLD	98%
No MAFLD - MAFLD	1.7%
No MAFLD – MAFLD with fibrosis	0.3%
MAFLD – no MAFLD	65.8%
MAFLD - MAFLD	28.9%
MAFLD – MAFLD with fibrosis	5.3%
MAFLD with fibrosis - MAFLD	10%
MAFLD with fibrosis – MAFLD with fibrosis	0%

Key findings

- The highest risk of MAFLD progression - PWH with MAFLD with BMI >25 kg/m^2.
- The highest risk of fibrosis progression - PWH with MAFLD with BMI >25 kg/m^2.
- The highest probability of MAFLD reversibility – PWH with lean MAFLD.
- The highest probability of fibrosis reversibility – PWH with diabetes.

Conclusions

- Use of Markov models depicts dynamic changes of FLD with or without fibrosis over time.
- MAFLD categories offer the possibility to stratify PWH at highest risk of hepatic and extra-hepatic adverse outcomes.

WEEK 48 METABOLIC HEALTH AFTER SWITCH TO DTG/3TC VS CAR BY BASELINE REGIMEN (SALSA)

Debbie Hagins,[1] Cristina Mussini,[2] Fujie Zhang,[3] Princy N. Kumar,[4] Laurent Hocqueloux,[5] Nuria Espinosa,[6] Christoph Wyen,[7] James Oyee,[8] Lori A. Gordon,[9] Gilda Bonnampo,[9] Brian Wynne,[9] Elizabeth Blot,[9] Mounir Ait-Khaled,[10] Jean van Wyk[10]

603

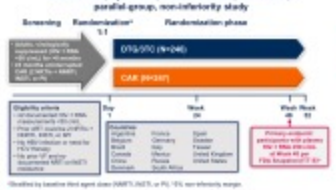
Background

- International treatment guidelines recommend DTG/3TC for treatment-naive and treatment-experienced PLWH[1-3]
- Switching to the 2-drug regimen DTG/3TC fixed-dose combination was non-inferior to continuing various 3- or 4-drug current antiretroviral regimens (CAR) in virologically suppressed adults with HIV-1, with no confirmed virologic withdrawals and a good safety profile[4]
- Here we present Week 48 metabolic health results (post hoc) from SALSA

Methods

- SALSA is a phase 3 randomized trial comparing switching to DTG/3TC vs continuing CAR (Figure 1)

Figure 1. SALSA Phase 3 Study Design



*Stratified by baseline third agent class (INSTI, NNRTI, or PI); †FDA non-inferiority margin

- Adjusted mean change from baseline to Week 48 for weight, fasting lipids, insulin resistance (measured by changes in glucose, insulin, HbA_{1c}, and HOMA-IR), and liver fibrosis (measured by FIB-4) were compared between treatment groups using mixed-model repeated measures (MMRM) in the overall SALSA population and by baseline TAF or TDF use, with the CAR group as reference for all analyses
- For metabolic syndrome (using the International Diabetes Federation definition),[5] HOMA-IR ≥2, and FIB-4 ≥1.45, logistic regression model adjusting for relevant baseline variables was used for comparison between treatment groups

Acknowledgments: This study was funded by ViiV Healthcare. We thank the study participants, their families and caregivers, investigators and site staff who contributed to the study, and the ViiV Healthcare, GlaxoSmithKline, and Pharmaceutical Product Development study team members. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by BioScribe, LLC and funded by ViiV Healthcare.

References: 1. DHHS. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2021. 2. EACS. EACS guidelines version 11.0. 2021. 3. Saag MS, et al. JAMA. 2020;324:1651-1669. 4. Cahn P, et al. Lancet HIV. 2021;8:e44-e54. 5. Virtual. Global Diabetes Federation. 2006.

One year after switching to DTG/3TC vs continuing 3-/4-drug CAR, weight gain was greater among participants switching from TDF-containing regimens and similar for TAF-containing regimens; in the overall population and baseline TDF or TAF use subgroups, **other metabolic health parameters were similar between DTG/3TC and CAR**

Results

Participants

- In the ITT-E population, 493 participants were randomized to switch to DTG/3TC (N=246) or continue CAR (N=247)
- Demographics, baseline characteristics, and baseline TAF or TDF use were similar between groups (Table 1)
  - Characteristics were similar between the baseline TAF and TDF use groups

Table 1. Baseline Demographics and Clinical Characteristics: ITT-E Population

Characteristic	DTG/3TC (N=246)	CAR (N=247)
Age, median (range), y	45 (22-74)	45 (23-65)
Female, n (%)	108 (44)	84 (34)
Race, n (%)		
African American/African heritage	45 (18)	48 (19)
Asian	31 (13)	39 (16)
White	149 (61)	144 (58)
Other race†	21 (9)	16 (6)
CD4+ cell count, median (range), cells/mm³	675 (164-2080)	668 (64-1954)
CD4+ cell count, cells/mm³, n (%)		
<500	80 (24)	83 (34)
≥500	166 (76)	164 (74)
Duration of ART before Day 1, median (range), mo	83 (4-240)	71 (10-253)
ART received at screening, n (%)		
TDF‡	109 (44)	100 (44)
BPV	66 (27)	66 (23)
TAF	83 (34)	61 (27)
Bictegravir/INSTI (BIC, DTG,§ or RAL)	27 (11)	30 (13)
Boosted INSTI (BVEAs)	24 (10)	25 (11)
Weight, median (range), kg	73 (43-136)	75 (39-165)
BMI, median (range), kg/m²	25 (16-51)	25 (14-55)
Metabolic syndrome, n (%)¶	20 (8)	35 (14)
Fasting insulin, geometric mean (95% CI)	1.93 (1.79-2.10)	2.13 (1.92-2.35)
Fasting glucose, median (range), mmol/L	5.0 (3.7-16.3)	5.2 (3.2-16.7)
HbA_{1c}, median (range)	5.3 (3.7-9.6)	5.4 (3.7-12.1)
HOMA-IR, median (range)	1.94 (0.45-15.9)	2.23 (0.40-45.88)

†Includes American Indian or Alaska Native or individuals of multiple races. ‡Includes tenofovir disoproxil fumarate (TDF)/3TC, n = 1 CAR; n = 0, 3TC regimens; unk (b): ETR + FTC + TAF (DTG/3TC, 1246 (n.3); CAR, 3247 (5); 3TC + FTC + TAF (BIC/3TC, 0246 (0); CAR, 1246 (1); 3TC + FTC + TAF + BIC + FTC + RGR (DTG/3TC, 1 (n.5); CAR, 0 (0). §Participants who have DRA ≥50 copies/mL and subtly any 2 of the nucleos(t)ide/c factors within the baseline and window: noted triglycerides, ≥150 mg/dL or treatment; reduced HDL, <40 mg/dL (men), <50 mg/dL (women), or treatment; raised blood pressure, systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or treatment for hypertension; raised fasting plasma glucose, ≥100 mg/dL or previous diagnosis of type 2 diabetes.

Weight Changes

- Overall, adjusted mean change in weight from baseline to Week 48 was 2.1 vs 0.6 kg in the DTG/3TC vs CAR groups (treatment difference, 1.49 kg; 95% CI, 0.73-2.28); weight change was similar between groups in participants with baseline TAF use and was greater in the DTG/3TC group for those with baseline TDF use (Figure 2)

Figure 2. Adjusted Mean Change in Weight From Baseline to Week 48 by Baseline TAF or TDF Use

*Treatment difference (95% CI) displayed above treatment groups. †Adjusted mean is the estimated mean change from baseline at Week 48 in each group calculated from MMRM adjusting for treatment, visit, baseline third agent class, CD4+ cell count, age, sex, race, baseline value, prior TDF/3TC, subgroup, treatment-by-visit interaction, baseline value-by-visit interaction, treatment-by-subgroup interaction, subgroup-by-visit interaction, and subgroup-by-treatment-by-visit interaction.

- In the overall analysis, proportion of participants with ≥10% weight gain was 12% (27/230) vs 4% (9/224) in the DTG/3TC vs CAR groups, respectively
- Proportions of participants with ≥10% weight gain were similar in the baseline TAF use subgroup [DTG/3TC, 8% (5/79) vs CAR, 7% (6/86)] and higher with DTG/3TC vs CAR [14% (14/98) vs 3% (3/95)] in the baseline TDF use subgroup

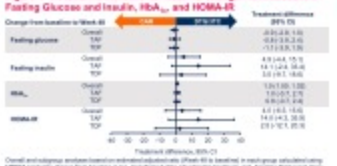
Metabolic Health Outcomes

- Changes in lipid parameters overall and analyzed by baseline TAF or TDF use were small and similar between the DTG/3TC and CAR groups (Figure 3)
  - Overall, adjusted mean percent changes from baseline using $\log_e$-transformed data in the DTG/3TC vs CAR groups, respectively, were the following: total cholesterol, 0.8% vs 1.9%; HDL-C, −0.8% vs 1.4%; LDL-C, 2.5% vs 3.0%; triglycerides, −3.3% vs −3.4%; and total cholesterol/HDL-C ratio, 1.8% vs 0.3%

Figure 3. Percent Change From Baseline in Fasting Lipids at Week 48 by Baseline TAF or TDF Use

- Adjusted mean changes in fasting glucose, fasting insulin, HbA_{1c}, and HOMA-IR were generally similar between groups (Figure 4)

Figure 4. Treatment Difference for Week 48 Change From Baseline in Fasting Glucose and Insulin, HbA_{1c}, and HOMA-IR



- Adjusted odds of HOMA-IR ≥2 at Week 48 were similar between treatment groups in the overall analysis (OR, 1.82; 95% CI, 0.63-1.90) and by baseline TAF (2.36; 0.81-4.66) or TDF use (0.58; 0.26-1.22)
  - Higher baseline HOMA-IR (OR, 1.19; 99% CI, 1.08-2.13) and BMI (1.14; 1.07-1.23) were associated with increased odds of HOMA-IR ≥2 at Week 48
- Adjusted change from baseline to Week 48 in FIB-4 was similar between groups in the overall analysis (treatment difference, −1.6; 95% CI, −5.7, 2.8) and in the baseline TAF (−2.2; −8.9, 5.0) and TDF use (−3.6; −9.7, 2.9) subgroup analyses
- In the overall analysis, adjusted odds of FIB-4 ≥1.45 were similar between treatment groups (OR, 1.07; 95% CI, 0.48-2.58)
  - Odds of FIB-4 ≥1.45 were lower in female vs male participants and higher with increased age and baseline FIB-4
- Adjusted odds of metabolic syndrome events were similar between groups in the overall (DTG vs CAR: OR, 1.38; 95% CI, 0.63-2.99) and subgroup analyses (DTG vs CAR: baseline TAF use, 1.56; 0.46-5.27; baseline TDF use, 1.49; 0.41-5.41; Figure 5)
  - Odds of metabolic syndrome events were higher among Black/African American (vs White) participants and those with (vs without) baseline hypertension, baseline high- (vs normal) triglycerides, low (vs normal) HDL-C, and baseline HOMA-IR ≥3 (vs <2)

Figure 5. Logistic Regression Analysis of Treatment Differences and Baseline Variables Associated With Metabolic Syndrome Events at Week 48

Conclusions

- At Week 48, differences in weight change from baseline after switching to DTG/3TC were observed among participants switching from TDF-containing regimens but not among those switching from TAF-containing regimens
- Although weight differed by baseline NRTI use, changes in other metabolic health parameters were small and similar between treatment groups in the overall and subgroup analyses
- Comprehensive evaluation of metabolic outcomes remains important for management of PLWH

Conference on Retroviruses and Opportunistic Infections; February 12-16, 2022; Virtual

Presenting Author: Debbie Hagins, debbie.hagins@bih.ga.gov

METABOLIC PERTURBATIONS BY INTEGRASE INHIBITORS IN DIFFERENTIATED HUMAN ADIPOCYTES

R. Taylor Pickering[1], Kaitlin Soden[1], Archana Asundi[1], Nina Lin[1]
[1]Boston Medical Center, Section of Infectious diseases

BOSTON UNIVERSITY

BOSTON MEDICAL CENTER

Background

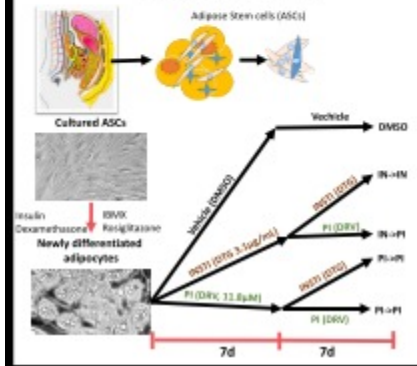
- Both HIV and antiretroviral (ARV) medications have dramatic effects on adipose tissue biology
- Integrase-Strand Transfer Inhibitors (INSTIs) have been implicated in excess weight gain among people living with HIV
- The effects of INSTIs on adipose tissue remain unclear

Objectives

- Examine the effects of INSTIs on aspects of adipose biology related to weight gain
- Determine if switching off INSTIs to other ARVs (protease inhibitors, PI) can reverse these effects

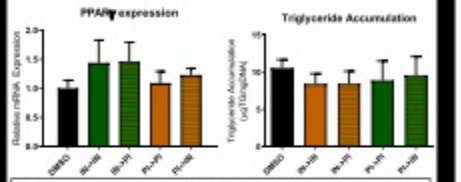
Methods

Culture and treatment of newly differentiated human adipocytes



Results

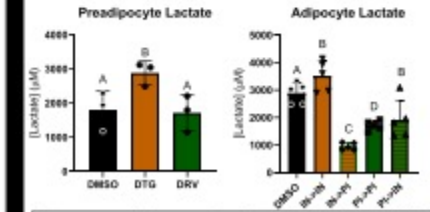
Treatment of newly differentiated adipocytes with ART does not alter markers of adipogenesis



mRNA Expression was determined using qRTPCR and normalized to DMSO; Triglyceride content was determined via enzymatic assay and normalized to DNA content. Data are derived from abdominal subcutaneous ASCs. n=10

Treatment of differentiated adipocytes with Dolutegravir resulted in media acidification

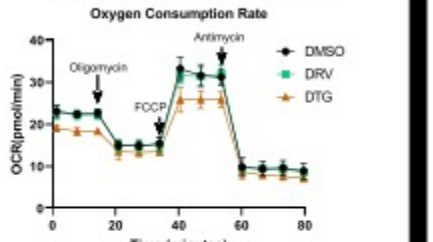
Dolutegravir increases lactate production in both preadipocytes and adipocytes



Lactate was measured using an enzymatic assay from 24 hour media incubations. Different letters indicate significant differences between conditions as determined by repeated measures ANOVA, p<0.05. n=5

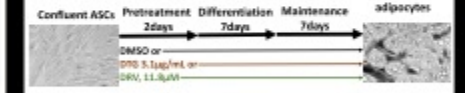
Results

Dolutegravir suppresses basal and maximal respiration rates in preadipocytes

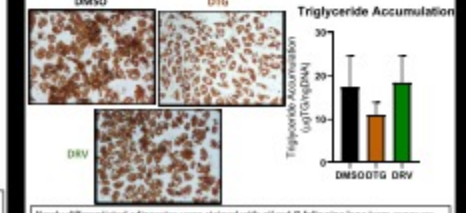


Preadipocytes were cultured in the presence of DMSO, Dolutegravir (DTG), or Darunavir (DRV) for 2 days prior to a Seahorse mitochondrial stress test. n=3

Does exposure during adipogenesis alter responses to ART?



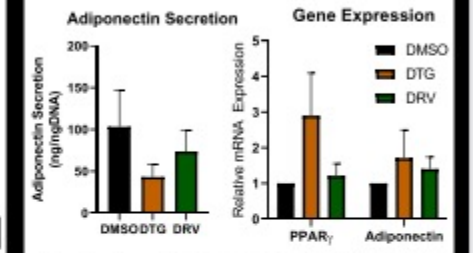
Exposure to Dolutegravir suppresses triglyceride accumulation in newly differentiated adipocytes



Newly differentiated adipocytes were stained with oil red O following long term exposure to vehicle, dolutegravir or darunavir. Triglyceride content was determined via enzymatic assay and normalized to DNA content. n=3

Results

Dolutegravir decreases adiponectin secretion despite changes in gene expression



Adiponectin secretion was determined using ELISAs and normalized to DNA content. mRNA Expression was determined using qRTPCR and normalized to DMSO). n=3

Summary/Conclusions

- INSTI exposure increased lactate production in both preadipocytes and mature adipocytes
- Dolutegravir decreased oxygen consumption of preadipocytes, indicating mitochondrial impairment
- INSTI exposure during differentiation reduced triglyceride accumulation and adiponectin secretion

Alterations in adipocyte metabolism and adipokine secretion may contribute to excess weight gain observed in people living with HIV taking integrase-strand transfer inhibitors

Acknowledgements/Support

Cells were obtained from the Boston Nutrition and Obesity Research Center (BNORC) Adipocyte Biology Core
Funding provided by the Clinical HIV/AIDS Research Training Program, T32 AI 052074

600

00599

ADIPOCYTE DIFFERENTIATION AND ANTIRETROVIRAL DRUGS: AN IN VITRO MODEL

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

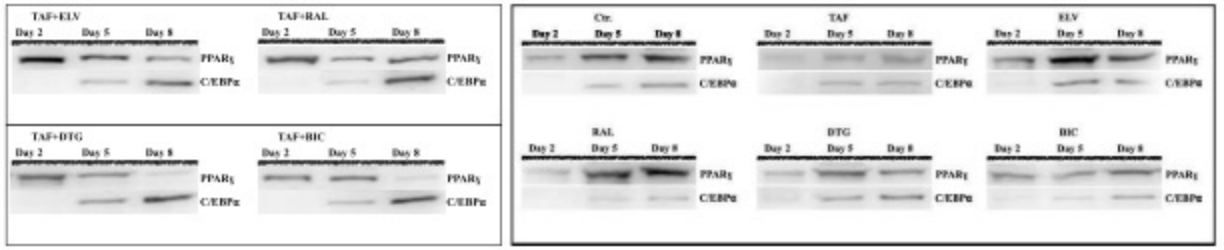
[1]Infectious Diseases and Gender Medicine Unit "D. Cotugno" Hospital – AO dei Colli, Naples Italy, [2]Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy, [3]Department of Sport Sciences and Wellness, University of Naples "Parthenope", Naples, Italy,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

BACKGROUND

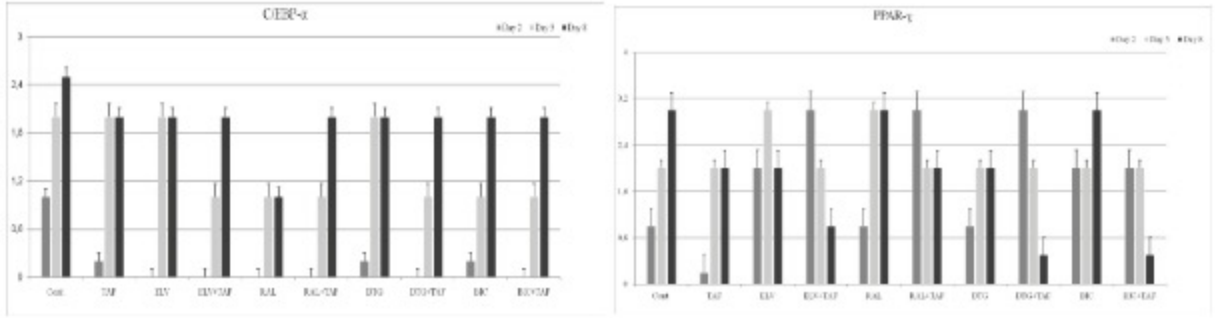
The Integrase Strand Transfer Inhibitors (INSTI) class of drugs is characterized by a good tolerability profile and a relatively high genetic barrier to HIV drug resistance. However, several studies reported greater weight gain among persons receiving INSTI-based regimens for initial therapy as compared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

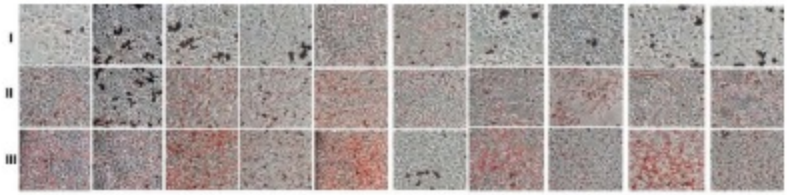
METHODS

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



Western Blot analysis showing different PPAR-γ and C/EBP-α expression levels according to different anti-HIV drugs





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

RESULTS

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

CONCLUSIONS

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

Author Contact Information: Vincenzo Esposito, Infectious Diseases and Gender Medicine Unit "D. Cotugno" Hospital – AO dei Colli, Via G. Quagliariello, 54 80131 Naples Italy. E-mail: vincenzoesposito@ospedalideicolli.it

ROSUVASTATIN WORSENS VITAMIN K2 STATUS WHICH IMPAIRS BENEFICIAL EFFECT ON BONE IN HIV

00610

Jared C. Durieux [1], Sokratis N. Zisis [2], Christian F. Mouchati [2], Grace A. McComsey [1,2]
[1]University Hospitals Cleveland Medical Center, Cleveland, Ohio, [2]Case Western Reserve University, Cleveland, Ohio

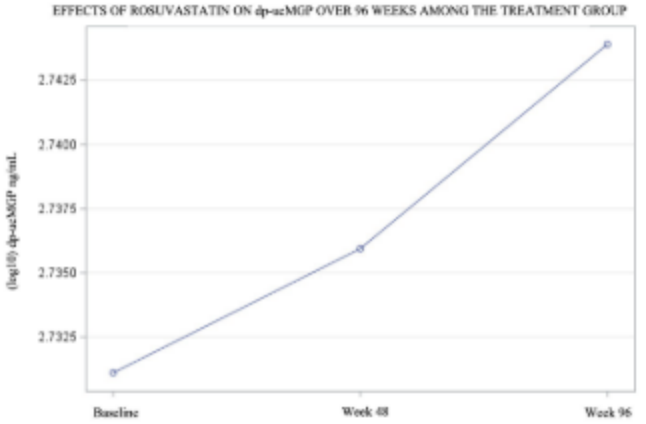
BACKGROUND

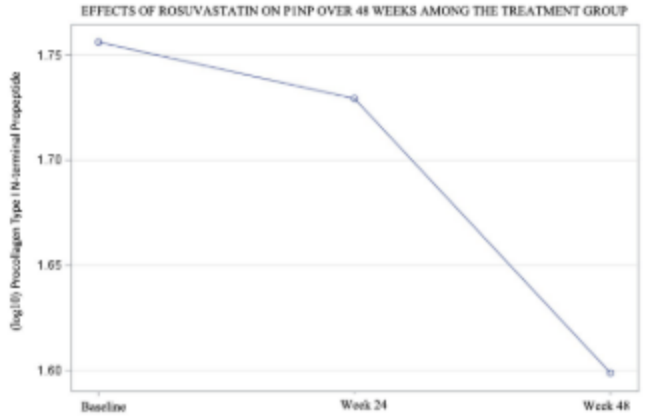
Vitamin K2 has shown a **positive effect on bone health** in the general population but has never been studied in HIV. Recent laboratory data suggested that statins impair vitamin K status, we investigated the **effects of Rosuvastatin on vitamin K** status in the 96-week *SATURN-HIV* clinical trail as a mechanism for the lack of long-term effect on bone health.

METHODS

- Data collected from participants randomized to placebo (n=75) or active treatment (n=72; **Rosuvastatin 10 mg daily**).
- Vitamin K-dependent dephosphorylated-uncarboxylated matrix Gla protein (**MGP**), a marker of K2 status **(poor K2 status=high MGP)**, and bone formation markers including N-terminal propeptide of type-1 collagen (**P1NP**) and osteocalcin (**OCN**) were obtained from plasma samples.
- Bone mineral density (**BMD**) measures of lumbar spine (L1-L4) and femoral neck were assessed by dual-energy absorptiometry.
- Constrained longitudinal analysis of covariance models were used to assess the effect of treatment on MGP, bone markers, and measures of BMD.

Rosuvastatin *increases* **MGP** levels (*worse* vitamin K2)





RESULTS

- *Pretreatment*:
  - Median MGP was 519.25 ng/mL (IQR: 451.15, 593.33)
  - Median P1NP was 54.27 ng/mL (IQR: 38.56, 67.95).
- *Week 48 (Active vs. Placebo)*:
  - **P1NP decreased** (p=0.04).
- *Week 96 (Active vs. Placebo)*:
  - **MGP increased** (p=0.03)
  - **Negative slope observed in femoral BMD** and **OCN** (p>0.05)
  - **Positive slope observed in TNFaRII** and **spine BMD** (p>0.05)

CONCLUSIONS

- **Rosuvastatin has a *negative effect* on vitamin K2 *and* P1NP** in people living with HIV on antiretroviral treatment.

Despite known benefits of statins in HIV, its **effects on bone health are less clear**. We provide evidence that **Rosuvastatin increases MGP, signaling worse vitamin K2** status. Research is needed on whether supplementation with vitamin K2 may be warranted in the setting of statin therapy to avoid unfavorable effects on bone.

Author Contact Information:
Jared C. Durieux, MS, MDS, MPH:
jared.Durieux@uhhospitals.org

PETRAM RESULTS: BONE TURNOVER CHANGES ON 18F-NaF PET/CT AFTER A RANDOMISED SWITCH TO TAF

CROI ID 00609

Amelia EB. Moore[1], James E. Burns[2], Deirdre Sally[2], Ana Milinkovic[2], Georgios Krokos[1], Joemon John[1], Christopher Rookyard[1], Erica Pool[2], Richard Gilson[2], Alejandro Arenas-Pinto[2], Gary Cook[1], David Dunn[2], Glen Blake[1], Sarah L. Pett[2]

[1]King's College London, London, United Kingdom, [2]University College London, London, United Kingdom

BACKGROUND

- The mechanism of bone loss in people living with HIV on antiretroviral therapy is poorly understood.
- Plasma bone turnover markers (BTMs) suggest uncoupling of bone resorption and formation by a treatment effect on bone cells [1].
- Switching away from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide fumarate (TAF)-containing regimens has been associated with bone mineral density (BMD) gains measured by dual-energy X-ray absorptiometry (DXA) [2]. One possible explanation is reversal of ongoing subclinical bone loss in the TDF to TAF switchers.
- Positron emission tomography (PET)/computed tomography (CT) with radiolabelled sodium fluoride (18F-NaF-PET/CT) imaging assesses regional bone formation to help differentiate between increased or decreased bone turnover at skeletal sites [3].

METHOD

- Open-label randomised 48-week trial, exploring regional bone formation at the hip and lumbar spine, as measured by 18F-NaF-PET/CT in patients switching to TAF-based ART regimen compared with those continuing a TDF-based regimen.
- Conducted at a single site in London, UK between 2019 and 2021

Primary Outcome: change in regional bone formation on 18F-NaF-PET/CT at the hip and lumbar spine between baseline and last study scan in those switching to TAF vs. continuing TDF.

Figure 1: PETRAM trial design

*Due to COVID-19, some scans were delayed. As such, scans were re-classified as 'baseline', 'mid-study', and 'last-study' scan.

PETRAM Study population

Key inclusion: HIV-1-positive cisgender males; Age 40-65yrs old; No known history of osteoporosis; On the fixed dose combination of TDF/emtricitabine(FTC)/rilpivirine (RPV) >24 weeks

Key exclusion: Current/previous treatment (within prior 12 months) that can affect bone metabolism

Radiological methodology

- 30-minute static 18F-NaF-PET/CT scan of the lumbar spine and hip was performed 1 hour after injection of 90 MBq of radiolabelled sodium fluoride (18F-NaF)
- A pre-PET CT scan provided attenuation correction of the PET images, and defined placement of the regions of interest for the PET scan analysis.
- A DXA scan measuring BMD at the lumbar spine, non-dominant hip and whole body was performed at the same 3 timepoints as the 18F-NaF-PET/CT.
- All 18F-NaF-PET/CT were performed on the same scanner at King's College London and Guy's and St. Thomas' PET Centre, all DXA performed on the same DXA scanner at the Osteoporosis unit at Guy's and St Thomas' NHS Foundation Trust.
- All scans were analysed by the same 2 experienced PET scientists blinded to the arm of randomisation of the participants.

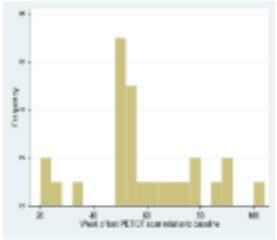
Bone biomarkers (exploratory end-point)

- Drawn at 3 study timepoints, batched and run at the Bioanalytical Facility, University of East Anglia for procollagen Type I N terminal propeptide (PINP) and cross-linked C telopeptides of Type I collagen (CTX).

COVID-19 mitigation

- The trial was severely affected by the SARS-CoV-2 pandemic, with delays in some baseline, week 24 and 48 scans, resulting in some 'week 24' scans being done when participants had been on study drug for 48 weeks (**Figure 2**)
- A protocol amendment in May 2021 therefore amended the primary outcome from the originally planned change in regional bone formation as measured by 18F-NaF-PET/CT at week 24, to change in regional bone formation between baseline and last scan.

Figure 2: Histogram showing the occurrence of the last scan for each participant relative to baseline



Sample size and statistical analysis

- Analysis of covariance (ANCOVA) adjusted for baseline value, study arm, and interval between baseline and last scan
- A sample of 30 (15 per arm) was estimated to provide 90% power to detect a mean change of 25% with SD of 20% in SUV between the arms.
- Change in bone biomarkers (CTX+PINP) is an exploratory outcome also analysed using ANCOVA.

RESULTS.

Table 1: PETRAM baseline characteristics

Characteristic		TAF (n=16)	TDF (n=13)	Total (n=29)
White ethnicity	n (%)	12 (75)	10 (77)	22 (76)
Age (years)	Mean (SD)	49.6 (5.3)	52.7 (4.8)	51.0 (5.2)
Years since HIV diagnosis	Mean (SD)	12.7 (5.8)	17.5 (7.8)	14.9 (7.1)
CD4+ T-cell count (cells/µL)	Mean (SD)	525 (162)	534 (152)	529 (155)
Duration of TDF/FTC/RPV use (months)	Mean (SD)	45 (22)	54 (16)	49 (20)
Weight (kg)	Mean (SD)	84.3 (12.9)	82.6 (6.2)	83.5 (10.3)
BMI (kg/m²)	Mean (SD)	25.8 (3.2)	25.1 (2.7)	25.5 (2.9)
FRAX score	Mean (SD)	3.4 (1.4)	3.1 (0.6)	3.3 (1.1)
T-score Femoral Neck	Mean (SD)	-0.8 (1.2)	-0.7 (0.8)	-0.8 (1.0)
Vitamin D				
Sufficient (>50 nmol/L)	n (%)	8 (50)	8 (61)	16 (55)
Insufficient (25-50 nmol/L)	n (%)	7 (44)	4 (31)	11 (38)
Deficient (<25 nmol/L)	n (%)	1 (6)	1 (8)	2 (7)

n=2 of vitamin D deficient and n=7 of insufficient started vitamin D supplementation

- The time between baseline and final scans ranged between 23-103 weeks (median 55).
- There ***was no significant difference in change of SUV*** at the lumbar spine or hip between arms (Figure 3a+b, Table 2)
- There was a ***trend towards improved spine BMD*** in the TAF arm (+2.0%, 0-4.0, p=0.06), but not total hip, (Figure 3c+d, Table 2)
- Exploratory ***analysis of bone biomarkers showed large reductions in the TAF arm*** compared to TDF, for CTX [-28.2% (-43.5, -13.0, p=0.006)] more-so than PINP [-10.6 (-29.3, 8.1, p=0.31)] (Figure 4a+b, Table 3).

Figure 3a-d: Baseline vs. last scan lumbar SUV (a), total hip SUV (b), total spine BMD (c), and total hip BMD (d)

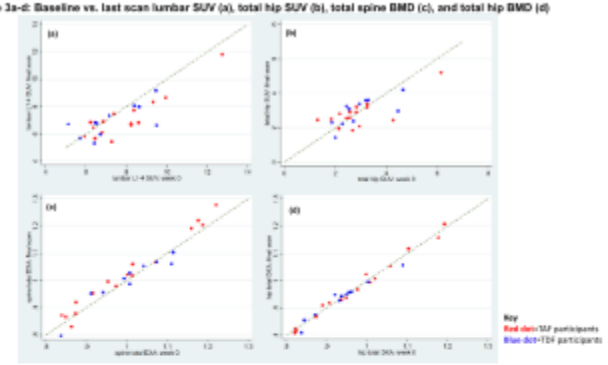


Table 2: Primary analysis of covariance of last-study 18F-NaF-PET/CT and DXA scans adjusted for delays in scans due to COVID-19. All participants with delayed scans remained on allocated treatment

Parameter	Baseline mean (SD)		Predicted relative change (%) at 48 weeks (95 % CI)		Relative % difference: TAF vs. TDF (95% CI)	P-value
	TAF	TDF	TAF	TDF		
Spine - SUV	7.8 (1.8)	7.3 (1.5)	-7.9 (-14.4, -1.5)	-5.3 (-12.1, 1.5)	-2.8 (-12.0, 6.5)	0.57
Hip - SUV	2.8 (1.1)	2.9 (0.9)	+0.3 (-12.2, 12.8)	+2.9 (-11.1, 16.9)	-2.6 (-19.4, 14.3)	0.77
Spine BMD	1.0 (0.1)	1.0 (0.1)	+1.7 (0.3, 3.1)	-0.3 (-1.8, 1.2)	+2.0 (0.0, 4.0)	0.06
Hip BMD	0.97 (0.12)	0.94 (0.07)	-0.2 (-1.1, 0.7)	-0.2 (-1.2, 0.8)	0.0 (-1.2, 1.4)	0.94

Figure 4a and b: Changes in bone biomarkers CTX (a) and PINP (b) by arm of randomisation

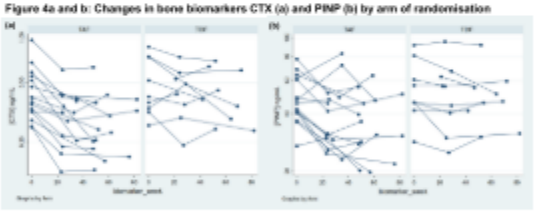


Table 3: Exploratory analysis of covariance of bone biomarkers CTX and PINP by arm of randomisation

Parameter	Baseline mean (SD)		Predicted relative change (%) at 24 weeks (95 % CI)		Relative % difference: TAF vs. TDF (95% CI)	P-value
	TAF	TDF	TAF	TDF		
CTX	0.44 (0.19)	0.51 (0.21)	-33.0 (-43.0, -23.1)	-6.7 (-23.2, 9.0)	-26.2 (-43.5, -13.0)	0.006
PINP	48.6 (13.6)	55.8 (18.8)	-18.6 (-30.5, -6.7)	-9.0 (-24.9, 6.8)	-10.6 (-29.3, 8.1)	0.31

CONCLUSIONS

- The reduction in bone biomarkers in the TAF arm, particularly CTX, ***suggests participants are moving from a high bone turnover state after switch.***
- This is supported by a decrease in SUV, which reflects a decreased rate of bone formation, and the trend towards increased spine BMD as bone lost during the high remodeling period is restored.
- The response is less in the hip than the spine, since this effect predominantly occurs in trabecular bone
- Overall, ***this pattern is similar to an individual with osteoporosis starting bisphosphonates***
- The lack of significant change in SUV may be from a lack of power.

References:

1. Odar et al. Bone Reports. 2020. https://doi.org/10.1016/j.bonr.2020.100727
2. Maggiolo et al. Lancet HIV. 2019. https://doi.org/10.1016/S2352-3018(19)30108-X
3. Frost et al. J Clin Densitom. 2007. https://doi.org/10.1016/j.jocd.2006.10.006

Acknowledgements: Our grateful thanks to all the PETRAM participants, and all PETRAM Co-Investigators at Mortimer Market Centre, and colleagues at the PET Centre and Osteoporosis Unit at Guy's and St Thomas' NHS Foundation Trust

Financial declaration: PETRAM (NCT #: 03409012) is funded by an independent academic grant in support of investigator initiated research from Gilead Sciences. Pett and Dunn receive funding in support of their salary from the Medical Research Council, United Kingdom (grant MC_UU_00004/03 and MC_UU_00004/04)

Contact: Professor Sarah. L Pett
s.pett@ucl.ac.uk.

Proteinuria Is Common Among People with HIV With Controlled Viremia

Edgar T Overton[1],Amy Kantor[2], Kathleen V. Fitch[3], Paul Muntner[1], Mosepele Mosepele[4], Judith A. Aberg[5],Carl J. Fichtenbaum[6], Grace A. McComsey[7], Carlos Malvestutto[8], Michael T. Lu[9], Pamela S. Douglas[10], Steven K. Grinspoon[3], Heather Ribaudo[2], Christina Wyatt[10], for the REPRIEVE Trial Investigators

1. Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL. 2. Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston MA. 3. Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA. 4. University of Botswana, Gaborone, Botswana. 5. Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY. 6. Department of Medicine for Translational Research, University of Cincinnati, Cincinnati, OH. 7. Case Western Reserve University, Cleveland, OH. 8. Division of Infectious Diseases, The Ohio State University Wexner Medical Center, Columbus, OH. 9. Harvard Medical School, Boston, MA. 10. Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC.

BACKGROUND

- When compared to the general population, PWH are at greater risk to develop CKD and end stage kidney disease.
- An assessment of urinary protein and albumin excretion, a marker of tubular and glomerular disease, respectively, can serve as an important prognostic measure of progression of CKD.
- Excess proteinuria and albuminuria serve as markers of kidney damage and are used to predict progression of kidney disease.

METHODS

- REPRIEVE (NCT02344290) is a randomized ASCVD prevention trial of PWH between ages 40 and 75 on stable ART.
- This is the baseline analysis report for the Kidney Ancillary Study to REPRIEVE. The analyses in this report examine of proteinuria and albuminuria and how these values vary by clinical risk factors.
- All analyses are limited to Kidney Ancillary Study population and include participants with samples drawn on or before the start of treatment, who enrolled in REPRIEVE A5332 after protocol version 3 at 42 sites participating in the Kidney Ancillary Study.
- Definitions:
  - **Proteinuria (urine protein to creatinine ratio):**
    - normal to mildly increased (<150mg/g)
    - moderately increased (150-500mg/g)
    - severely increased (>500mg/g)
  - **Albuminuria (urine albumin to creatinine ratio):**
    - normal to mildly increased (<30mcg/mg)
    - moderately increased (30-300mcg/mg)
    - severely increased (>300mcg/mg)
- *Statistical analysis:* We summarize participant characteristics overall and by urinary protein category. Single and multivariable log binomial regression was performed for each binary outcome. Moderately and severely increased were combined for modeling of proteinuria and albuminuria.

RESULTS

Table 1: Characteristics of Participants by Proteinuria Category

Characteristic*	Normal to Mildly Increased (n=1863)	Moderately Increased (n=656)	Severely Increased (n=74)
Age in years	49 (44 ,53)	49 (45, 54)	48 (44, 53)
Natal female sex	641 (36%)	327 (53%)	45 (61%)
Race			
White	641 (33%)	167 (25%)	18 (24%)
Black or African American	926 (47%)	318 (48%)	39 (53%)
Asian	289 (15%)	150 (23%)	14 (19%)
GBD Super Region			
High Income	1243 (63%)	296 (45%)	33 (45%)
Lat America/Caribbean	110 (6%)	32 (5%)	2 (3%)
Southeast/East Asia	272 (14%)	149 (23%)	14 (19%)
Sub-Saharan Africa	338 (17%)	179 (27%)	25 (34%)
Diabetes	11 (1%)	4(1%)	0 (0%)
Hypertension	589 (30%)	214 (33%)	20 (27%)
Obesity (BMI ≥ 30kg/m²)	507 (26%)	128 (20%)	13 (18%)
Current/former smoker	884 (45%)	284 (43%)	26 (36%)
eGFR (mL/min per 1.73m²)	98 (82,111)	99 (84,113)	91 (72,112)
Current CD4 ct (c/mm³)	629 (468, 826)	595 (437, 775)	609 (443, 778)
HIV VL <400 cp/mL	1638 (98%)	495 (98%)	56 (98%)

*Continuous variables are described as Median (Q1, Q3). Other variables reported as count and percentage. The HIV viral load data reflects missing values for 485 participants.

In the REPRIEVE cohort, proteinuria and albuminuria were present among 27% and 9% of PWH despite 98% having HIV VL < 400 cp/mL.

RESULTS

Figure 1: Distribution of Proteinuria Among 2693 Participants

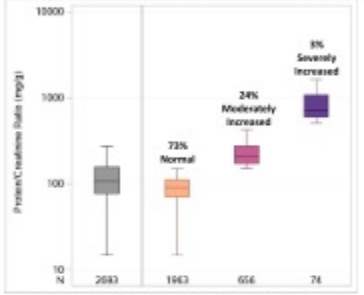


Figure 2: Distribution of Albuminuria Among 2791 Participants

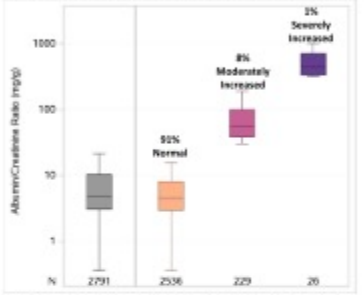


Figure 3: Adjusted Relative Risk of Elevated Proteinuria

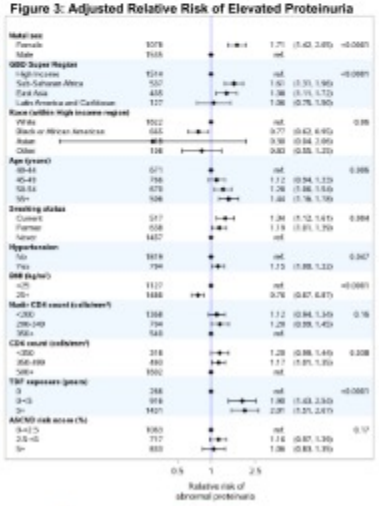
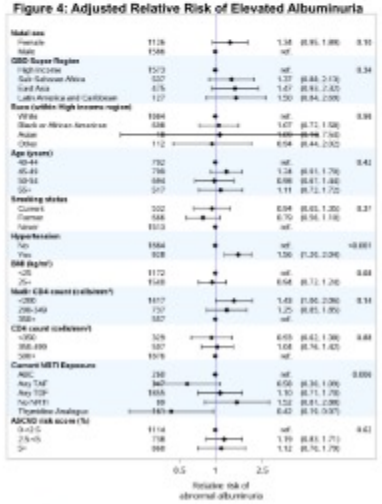


Figure 4: Adjusted Relative Risk of Elevated Albuminuria



FINDINGS

- Among REPRIEVE participants in the Kidney Ancillary Study, all were receiving ART, median CD4 count was 623 cells/mm³, 98% with HIV VL < 400cp/mL, eGFR 98 mL/min.
- The baseline prevalence of proteinuria and albuminuria was 27% and 9%, respectively.
- For participants with severely increased proteinuria, median eGFR was lower than for other groups (91 vs 98 mL/min). This was not observed among participants with severely increased albuminuria.
- Women were more likely to have excess proteinuria compared to men (35% vs. 21%) and albuminuria (11% vs. 8%).
- 38% and 37% of participants from Sub-Saharan Africa and Asian sites, respectively, had excess proteinuria. Similarly, albuminuria was more common from these sites compared to High Income regions.
- Among participants receiving tenofovir disoproxil fumarate, 32% had excess proteinuria and 10% excess albuminuria.
- Nadir and current CD4 counts were numerically lower for persons with excess proteinuria.
- In adjusted analysis, these factors remained associated with proteinuria (Fig 3):
  - Female sex
  - Enrollment from Sub-Saharan Africa and Asian sites
  - Older age
  - Current smoking
  - Diagnosis of hypertension
  - BMI < 25 kg/m²
  - Exposure to tenofovir disoproxil fumarate
- In adjusted analysis, these factors remained associated with albuminuria (Fig 4):
  - Diagnosis of hypertension
  - Certain NRTI exposures

CONCLUSIONS

- The proportion of PWH with suppressed viremia in the REPRIEVE cohort with excess proteinuria was 27%, a significant proportion of the cohort.
- Several factors related to excess proteinuria were as previously reported, including older age, diagnosis of hypertension, current smoking, and use of tenofovir disoproxil fumarate.
- The association with female sex and enrollment from Sub-Saharan Africa and Asian sites require additional analysis and an assessment of why these differences were noted. Potential explanations include:
  - Exposure to additional factors causing proteinuria.
  - Lack of access to prevention services.
- Excess albuminuria was present in 9% of the cohort.
  - Hypertension was independently associated with albuminuria.
  - There were also differences based on NRTI use.
- Future analyses will focus on the relationship of excess proteinuria and albuminuria or progressive kidney function declines and the role of statins to prevent CKD.

ADDITIONAL KEY INFORMATION

Funding: This work was supported by the National Institutes of Health (UB1HL123338 and U01HL123339); Knva Pharmaceuticals; Gilead Sciences; ViiV; the National Institute of Allergy and Infectious Diseases (UM1 AI068636 and UM1 AI106701); National Institute of Diabetes and Digestive and Kidney Diseases (grant number R01 DK108430); and National Heart, Lung, and Blood Institute (grant number P30DK 040561)

Author Contact Information:
Edgar T. Overton
Phone: 205-996-2373
Email: eoverton@uabmc.edu

Acknowledgements: We gratefully thank the study participants, site staff, and study-associated personnel for their ongoing participation in REPRIEVE.

PREVALENCE OF ANEMIA AND RISK FACTORS IN PEOPLE WITH HIV IN THE MODERN ART ERA

Raynell Lang[1], M. John Gill[2], Richard Moore[3], Michael J. Silverberg[4], Amy Justice[5], Amanda Willig[6], Angel Mayor[7], Marina B. Klein[8], Michael A. Horberg[9], Kelly Gebo[3], Ronald J. Bosch[10], Laura Bamford[11], Jennifer S. Lee[1], Keri N. Althoff[1], for the NA-ACCORD of IeDEA

[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2]Southern Alberta Clinic, Calgary, Canada, [3]The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [4]Kaiser Permanente Division of Research, Oakland, CA, United States, [5]Yale School of Medicine & VA Connecticut Healthcare System, West Haven, USA, [6]University of Alabama at Birmingham, Birmingham, AL, United States, [7]Universidad Central del Caribe, Bayamon, Puerto Rico, [8]McGill University Health Center, Montreal, Canada, [9]Kaiser Permanente Mid-Atlantic States, Rockville, MD, United States, [10]Harvard TH Chan School of Public Health, Boston, MA, United States, [11]University of California San Diego School of Medicine, La Jolla , USA

Contact
Name: Raynell Lang
E-mail: Raynell.Lang@ahs.ca

#614

@NAACCORD @iedeaglobal

Introduction

- In the modern ART era, anemia is less common in people with HIV (PWH) however, its prevalence and risk factors remain largely unknown.
- As anemia is an independent predictor of increased morbidity and mortality in PWH, we aimed to estimate its prevalence and examine the clinical and laboratory associations with anemia in both males and females.

Methods

- Using the NA-ACCORD, we estimated the annual prevalence between January 1, 2007- December 31, 2017 of anemia in PWH categorized as;
  - Mild (11.0-12.9g/dL males, 11.0-11.9g/dL females)
  - Moderate (8.0–10.9g/dL)
  - Severe (<8.0g/dL)
- Poisson regression models with robust variance estimated crude and adjusted prevalence ratios (aPR) and 95% confidence intervals comparing risk factors for those ever having a measure of no/mild anemia vs. moderate/severe anemia (outcome) during the study period.
- It was anticipated that risk factors would vary by sex, therefore results were stratified by sex.
- Time-fixed: age, sex, race/ethnicity, HIV acquisition risk, BMI, diabetes, hypertension, high cholesterol, chronic kidney disease, statin use, AIDS diagnoses, Hepatitis C (HCV) and B (HBV) infection at or prior to study entry.
- Time-varying: low (≤200cells/mm³) CD4 count and unsuppressed HIV RNA (>200 copies/mL) per calendar year; if there were multiple measurements per year, the median was used.
- Antiretroviral (ART) use (including AZT), ribavirin or interferon use was defined as use anytime during the month of hemoglobin measure.

Despite decreasing over time, the prevalence of anemia among PWH is higher than that reported in the general population of high-income countries (~5%). There was a higher burden of anemia in PWH seen among those with low CD4 counts, emphasizing the importance of effective ART.

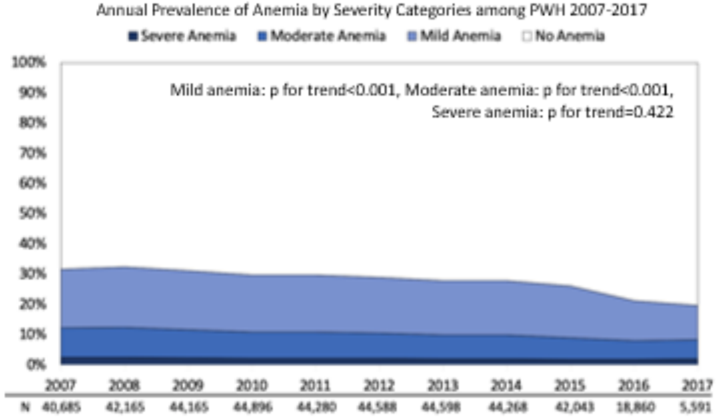
Results

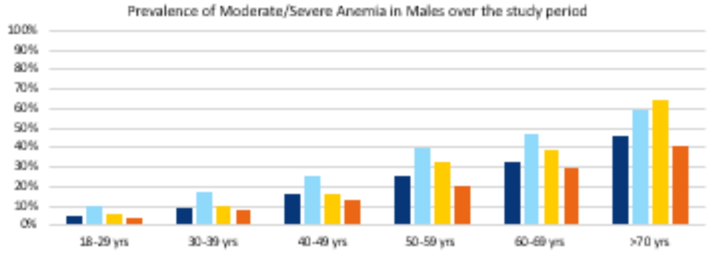
- Among 84,119 PWH, over the study period, 41,964 (49.9%) had at least one measure of anemia with 20,379 (24.2%) having mild anemia, 14,936 (17.8%) moderate anemia and 6,649 (7.9%) severe anemia.
- The average annual prevalence of anemia was 29.1% over the study period, this decreased from 2007 to 2017 (see shaded area plot).
- The risk of moderate/severe anemia was higher in females, Non-Hispanic Black and Hispanic PWH compared to Non-Hispanic White PWH, those underweight, with comorbidities and low CD4 counts (see bar charts and table).
- Aging increased anemia risk among males, but not females (see table).

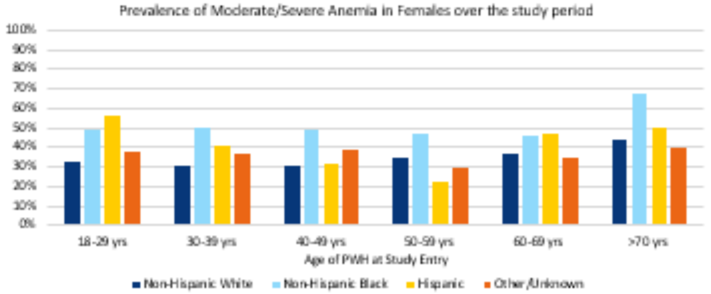
Crude (cPR) and adjusted (aPR) prevalence ratios of risk factors associated with moderate or severe anemia compared to mild or no anemia

Characteristic	cPR, 95% CI (N=84,119)		aPR, 95% CI (N=84,119)		aPR Males, 95% CI (N=74,119)		aPR Females, 95% CI (N=10,000)	
Age (per 10 year increase)	1.33	1.32-1.34	1.15	1.14-1.17	1.24	1.22-1.25	0.91	0.89-0.93
Sex								
Female	1.88	1.83-1.93	1.91	1.85-1.97	-	-	-	-
Race and ethnicity								
Non-Hispanic White	Ref		Ref		Ref		Ref	
Non-Hispanic Black	1.66	1.62-1.71	1.26	1.23-1.29	1.21	1.18-1.25	1.48	1.39-1.58
Hispanic	1.04	0.99-1.09	1.09	1.04-1.13	1.07	1.02-1.12	1.16	1.07-1.33
Other/unknown	0.83	0.78-0.88	0.95	0.90-1.01	0.93	0.87-0.99	1.15	1.03-1.29
BMI								
Underweight	2.15	2.09-2.21	1.46	1.41-1.51	1.48	1.43-1.54	1.27	1.17-1.37
Normal Range	Ref		Ref		Ref		Ref	
Overweight/Obese	0.72	0.67-0.71	0.73	0.72-0.75	0.69	0.67-0.71	0.88	0.84-0.93
Hepatitis B infection	1.27	1.21-1.33	1.11	1.07-1.16	1.13	1.08-1.18	1.06	0.95-1.18
Hepatitis C infection	1.90	1.85-1.94	1.20	1.17-1.24	1.24	1.21-1.28	1.12	1.04-1.19
Detectable Viral Load	1.28	1.24-1.31	1.04	1.02-1.07	1.08	1.05-1.11	0.99	0.94-1.04
Low CD4 count	2.52	2.46-2.58	1.91	1.86-1.95	1.98	1.93-2.04	1.60	1.52-1.68
No ART	0.94	0.83-1.06	0.99	0.88-1.12	1.11	0.94-1.32	0.77	0.55-1.07

Adjusted models include age, sex, year enrolled into cohort, race/ethnicity, HIV acquisition risk, BMI, diabetes, hypertension, high cholesterol, chronic kidney disease, smoking status, statin use, AIDS diagnoses, Hepatitis C (HCV) and B infection, Low (≤200cells/mm³) CD4 count, unsuppressed HIV RNA (>200 copies/mL), ART use, AZT, ribavirin or interferon use.
Missing BMI, viral load, CD4 and ART use and smoking status variables were imputed using multiple imputation.







Acknowledgements

[illegible]

MACS
MULTICENTER AIDS COHORT STUDY

Sleep and Frailty Among Men with and Without HIV

Poster #0620

Mary C. Masters[1], Benjamin Barrett[2], Gypsyamber D'Souza[2], Joshua Hyong-Jin Cho[3], Sanjay R Patel[4], Valentina Stosor[1], Naresh M. Punjabi[5], Frank J. Palella[1],
[1]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Johns Hopkins University, Baltimore, MD, USA; [3]University of California, Los Angeles, CA, USA; [4]University of Pittsburgh, Pittsburgh, PA, USA; [5]University of Miami, Miami, FL, USA.

Northwestern Medicine

BACKGROUND

- Persons with HIV (PWH) experience earlier onset and increased rates of frailty compared to persons without HIV.
- Poor sleep has been associated with frailty in the general population.
- The goal of the current study was to examine associations between objective sleep measures and the existence of frailty among PWH.

METHODS

Study Participants

- The Multicenter AIDS Cohort Study (MACS) has been a large ongoing prospective observational cohort study of men living with HIV (MLWH) and demographically similar HIV-uninfected men who have sex with men.
- All MACS participants underwent semi-annual Fried Frailty phenotype assessments (grip strength, gait speed, activity, exhaustion, and weight loss).
- In 2018, a subset of MACS participants underwent in-home polysomnography using the Nox A1 sleep monitor.

Evaluations and Definitions

- Frailty is defined as simultaneously having≥ 3 Fried criteria.
- Sleep measures:
  - Total sleep time
  - Sleep efficiency (i.e., total sleep time/time in bed)
  - Wake after sleep onset (i.e., time awake after sleep onset).
  - Sleep measures were dichotomized by median cut-point.

Data Analysis

- Cross-sectional associations between sleep measures and temporally nearest measure of frailty (median [IQR] difference = 1 day [0-21 days]) were examined using Poisson regression models with robust variance estimates and adjusted for age, BMI, and type 2 diabetes.
- Models were also adjusted for HIV serostatus.

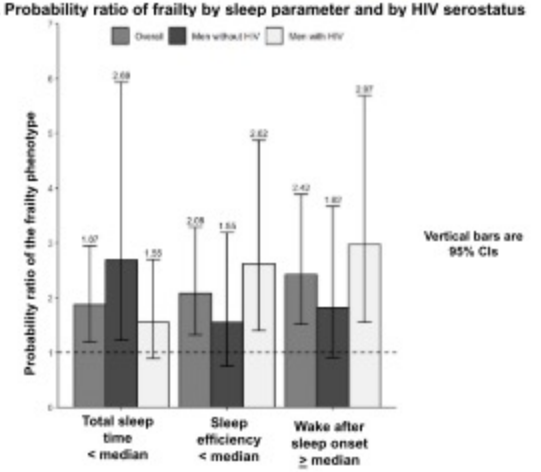
Objective measures of poor sleep were associated with greater frailty prevalence regardless of HIV serostatus. Associations between specific sleep parameters and frailty differed by HIV serostatus.

RESULTS

Table. Participant Characteristics by HIV Serostatus

Characteristic	Men without HIV (N = 356)	Men living with HIV (N = 446)
Frailty phenotype	30 (8%)	49 (11%)
Age in years, median (IQR)	63.0 (56.5-68.7)	56.3 (49.2-63.6)
BMI (kg/m^2), median (IQR)	27.0 (24.1-30.7)	26.5 (23.4-30.2)
Type 2 diabetes	130 (38%)	187 (44%)
Suppressed HIV viral load		423 (96%)
Current CD4 cell count, median (IQR)		704.5 (526.0-912.0)
Total sleep time	162 (46%)	236 (53%)
< Median, 382 minutes		
Sleep efficiency	163 (46%)	224 (50%)
< Median, 93%		
Wake after sleep onset	179 (50%)	224 (50%)
≥ Median, 33 minutes		

Figure. Probability ratio of frailty by sleep parameter and by HIV serostatus



CONCLUSIONS

- Objective measures of poor sleep were associated with greater frailty prevalence.
- Shorter total sleep time was associated with greater frailty prevalence among men without HIV, but not MLWH.
- Lower sleep efficiency and more nighttime awakening were associated with frailty among MLWH but not men without HIV.
- Interventions to improve sleep efficiency and reduce sleep fragmentation may represent approaches to prevent or treat frailty among MLWH.

ACKNOWLEDGEMENTS

We thank the study participants and site staff for their ongoing dedication.
The study was supported by the NIH: NIA (ROAG067390 to NICM. The MACS is funded primarily by NIAID, with additional cofunding from the NCI, NIDA, and NIMH. MACS (Principal Investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick, Todd Brown), U01-AI035042; Northwestern University (Steven Wolinsky), U01-AI035039; University of California, Los Angeles (Roger Detels, Otoniel Martinez-Maza, Otto Yang), U01-AI035040; University of Pittsburgh (Charles Rinaldo, Lawrence Kingsley, Jeremy Martinson), U01-AI035041; CAMACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson, Gypsyamber D'Souza), U01-AI035043.

CROI 2022
P00618
Post-CROI 2022

The FUNCFRAIL Score to discriminate Frailty in Older Adults with HIV

Matilde Sánchez-Conde[1], Antonio Antela[2], Jorge Vergas[3], Margarita Ramírez[4], Pablo Ryan[5], Fernando Dronda[1], Maria José Galindo[6], Miguel Torralba[7], Mª Jesús Bustinduy[8], Alfonso Cabello[9], Carmen Busca[10], Isabel Machuca[11], Fátima Brañas[5]

[1]Hospital Ramón y Cajal, Madrid, [2]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, [3]Hospital Universitario Clínico San Carlos, Madrid, [4]Hospital General Universitario Gregorio Marañón, Madrid, [5]Hospital Universitario Infanta Leonor, Madrid, [6]Hospital Clinic of Valencia, [7]Hospital Universitario de Guadalajara, Guadalajara, [8]Hospital Donostia, San Sebastián, [9]Fundacion Jimenez Diaz, Madrid, [10]Hospital La Paz, Madrid, [11]Hospital Reina Sofía, Córdoba. SPAIN

Author Contact Information:
msconde@gmail.com
@mscondetoledo

FUNCFRAIL

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
Instituto de Salud Carlos III
FEDER Fondo Europeo de Desarrollo Regional
UNIÓN EUROPEA "Una manera de hacer Europa"
FSG FUNDACIÓN SEIMC-GESIDA

marzo 2022 - NH Venezia Laguna Palace - Venezia Mestre

BACKGROUND

- The number of older adults with HIV is growing but data about this population are still scarce and mainly focused on comorbidity instead of on physical function and frailty.
- Frailty has a paramount importance because it has been related with worse clinical prognosis (morbidity, falls and death) but with a chance of success if detected.
- Different tools can be used to screen frailty but none of them have been developed specifically for the people with HIV.

OBJECTIVE

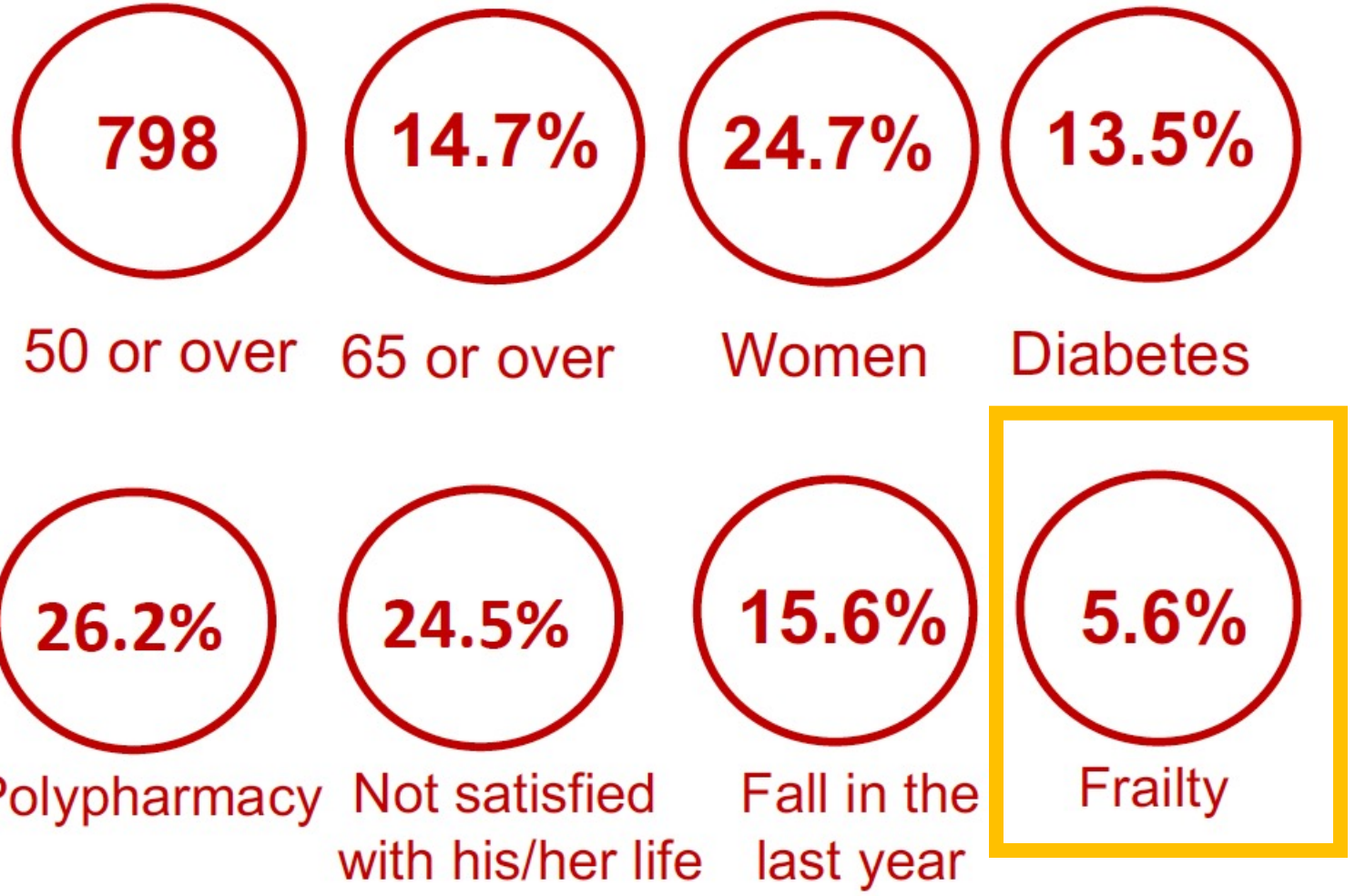
- Our objective was to develop a screening tool to discriminate frailty in older adults with HIV in a simple way in the daily practice.

METHODS

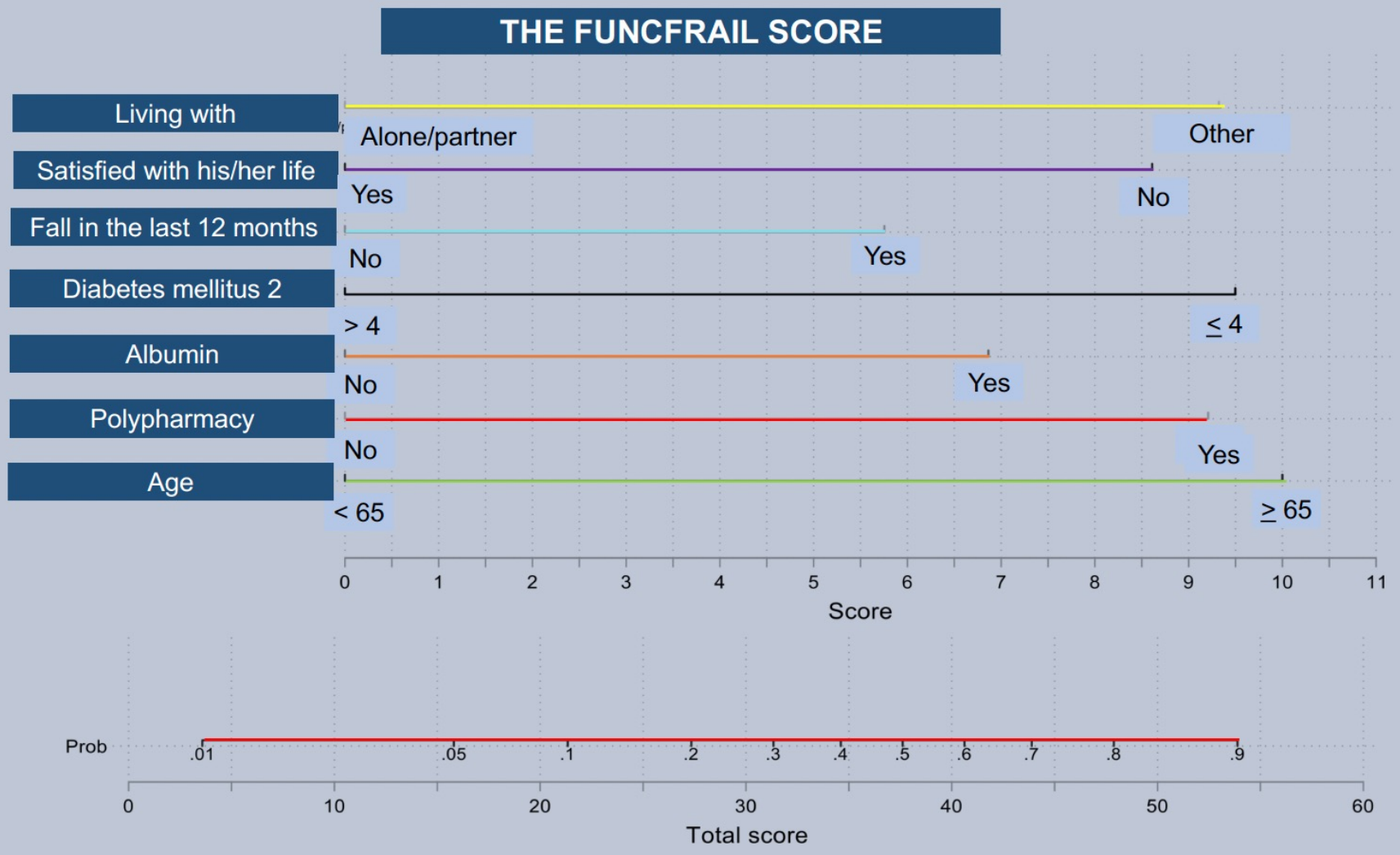
- Prospective multicenter longitudinal cohort: **the FUNCFRAIL Study.**
- Patients 50 or over with HIV were included.
- We recorded sociodemographic data, HIV infection-related data, comorbidities, and frailty, defined according to Fried's criteria.
- Multivariate logistic regression model was performed for those variables found to be associated with frailty in the univariate analyses to determine which were independently associated with frailty to estimate the predictive score (FUNCFRAIL Score). Frailty was treated as a binary variable: frailty vs prefrailty/robust.
- Discrimination for frailty prediction was estimated using the area under the ROC curve.

RESULTS

798 participants with the following main characteristics at the time of inclussion



RESULTS



Ranged from 0 to 11 points, with higher values indicating a greater likelihood of being frail

AUROC 95% to discriminate frail patients was 0,78 (0,71-0,85).

SCORE (points)

- Age 65 or over [+2]
- Polypharmacy [+2]
- Diabetes [+1]
- Albumin < 4 g/L [+2]
- Falls [+1]
- Not being satisfied with his/her life [+1]
- Not living alone or with a partner [+2]

Conclusions

- **The FUNCFRAIL Score is a simple tool to be used in daily clinical practice for frailty screening in older adults with HIV**

FUNCFRAIL

Spanish Cohort to Study Frailty and Physical Function in Older Adults with HIV.

CLINICAL CONDITIONS ASSOCIATED WITH PASC IN KAISER PERMANENTE MID-ATLANTIC STATES

Eric S. Watson[1], Michael A. Horberg[1], Celeena R. Jefferson[1], Julia M. Certa[1], Lily F Fathi[1], Mamta Bhatia[1], Keri N. Althoff[2], Carolyn F. Williams[3], Richard Moore[2]
[1]Kaiser Permanente Mid-Atlantic States, Rockville, MD, United States, [2]The Johns Hopkins University, Baltimore, MD, United States, [3]National Institute of Allergy and Infectious Diseases, Rockville, MD, United States

KAISER PERMANENTE® JOHNS HOPKINS UNIVERSITY

00627

BACKGROUND

- The natural history of the longer-term effects of SARS-CoV-2 (COVID-19), known as Post-Acute Sequelae of SARS-CoV-2 (PASC), is limited and not well defined.
- Disease characterization and definition changed over time and identification via standard diagnosis codes was only recently enacted.
- We aim to identify a cohort of individuals with PASC among Kaiser Permanente Mid-Atlantic States (KPMAS) members, and to identify the clinical conditions of greater burden for those with PASC.

METHODS

- We identified adult patients (≥18 years) who had a detectable SARS-CoV-2 RT-PCR result between 1/1/2020–12/31/2020.
- Diagnoses for these patients were pulled from our electronic health record system during Ambulatory, ED, or Virtual Visit encounters, that occurred in-person or virtually, with a physician
- Resulting diagnoses were grouped using AHRQ HCUP[1] Clinical Classification Software (CCS) to isolate conditions for PASC.
- Non-COVID CCS conditions were categorized into specific time intervals based on the first positive SARS-CoV-2 test as the index date (T_0), defined as:

  (1) "Prevalent": diagnoses in 4 years prior to T_0 and excluded from later consideration;
  (2) "Persistent/acute": new disease diagnoses 0-30 days post-T_0 and persisted 30-120 days further, and not included as prevalent;
  (3) "Incident/late": new disease diagnoses 30-120 days post-T_0, not previously identified as prevalent or persistent/acute.

- Final CCS distributions were computed relative to the condition counts for each time interval, validated by infectious disease physicians to identify conditions of focus (COF).

[1]Quality. AfHRa. HCUP Clinical Classification Software (CCS) for ICD-10 CM. . In:2019. https://www.hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp

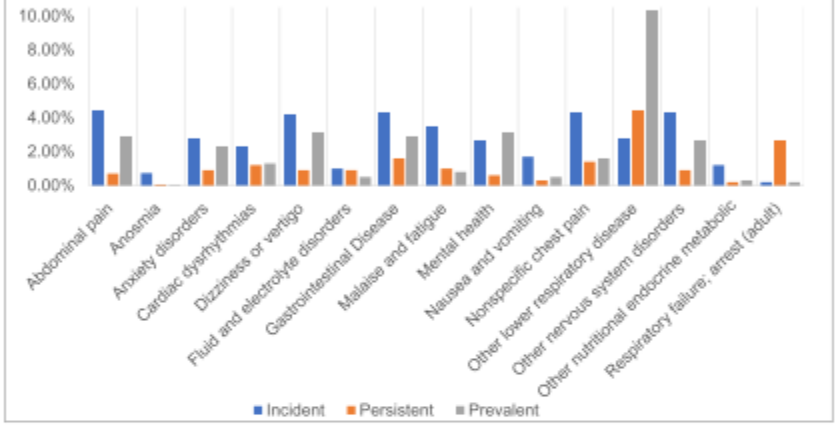
RESULTS

Table 1. KPMAS COVID(+) PCR Patient Demographics

Category	Detected Patient Population
Total, n(%)	31,390 (100.0%)
Gender, n(%)	
Female	17,631 (56.2%)
Male	13,759 (43.8%)
Age, n(%)	
18-29	6,279 (20.0%)
30-49	12,401 (39.5%)
50-64	9,014 (28.7%)
65+	3,696 (11.8%)
Race, n(%)	
Asian	3,191 (10.2%)
Black	12,120 (38.6%)
Hispanic	9,044 (28.8%)
White	5,425 (17.3%)
BMI, n(%)	
25-29.9 (Overweight)	7,252 (23.1%)
30-39.9 (Obesity)	9,042 (28.8%)
40+ (Severe Obesity)	2,591 (8.3%)
Comorbidities, n(%)	
CKD	921 (2.9%)
COPD	282 (0.9%)
Diabetes	5,998 (19.1%)
HIV	260 (0.8%)
Pregnant	569 (1.8%)
Tumor	790 (2.5%)
Hospitalization, n(%)	
Hospitalized at Index	2,330 (7.4%)
Hospitalized 30-120 days	540 (1.8%)

Figure 1. Clinical Classification Software (CCS) Distributions by Time Interval

	Abdominal pain	Anosmia	Anxiety disorders	Cardiac dysrhythmias	Dizziness or vertigo	Fluid and electrolyte disorders	Gastrointestinal Disease	Malaise and fatigue	Mental health	Nausea and vomiting	Nonspecific chest pain	Other lower respiratory disease	Other nervous system disorders	Other nutritional endocrine metabolic	Respiratory failure; arrest (adult)
Incident	4.4%	0.7%	2.8%	2.3%	4.2%	1.0%	4.3%	3.5%	2.7%	1.7%	4.3%	2.8%	4.3%	1.2%	0.2%
Persistent	0.7%	0.1%	0.9%	1.2%	0.9%	0.9%	1.6%	1.0%	0.6%	0.3%	1.4%	4.5%	0.9%	0.2%	2.7%
Prevalent	2.9%	0.0%	2.3%	1.3%	3.1%	0.5%	2.9%	0.8%	3.2%	0.5%	1.6%	10.4%	2.7%	0.3%	0.2%



Time intervals were defined as follows: Incident: 30-120 days post COVID+ test date; Persistent 0-30 days post COVID+ test date and persisted 30-120 days; Prevalent: 4 years prior to COVID+ test date

Incident and persistent conditions of significance associated with Post-Acute Sequelae of SARS-CoV-2 (PASC), such as Non-Specific Chest Pain and Respiratory Failure, are evident in a COVID positive cohort

LIMITATIONS

- Prevalent conditions are based on a 4-year prior history so capture of symptom-based conditions in the incident and persistent time intervals may be artificially reduced
- Significant changes in healthcare utilization and practice have occurred during our COVID based study period. Possible outcome of these changes include overall data capture, modifications to patient follow up and potential changes in patient behavior.
- Some diagnoses, like "Brain Fog", were not able to be captured from EHR diagnosis coding.

CONCLUSIONS

- We have identified conditions clinically associated with COVID-19, for both hospitalized and non-hospitalized patients, that persist from infection or present as incident beyond the acute COVID-19 period.
- This condition list can be utilized in clinical practice when following up with COVID-19 patients.

Funding through NIAID via Johns Hopkins and NA-ACCORD

ZINC DEFICIENCY IS INDEPENDENTLY ASSOCIATED WITH INCREASED COVID-19 DISEASE SEVERITY

643

Christian F. Mouchati [1], Sokratis N. Zisis [1], Jared C. Durieux [2], Sarah Scott [2], Beth Smith [2], Danielle Labbato [2], Grace A. McComsey [1]
[1]Case Western Reserve University, Cleveland, Ohio, [2]University Hospitals Cleveland Medical Center, Cleveland, Ohio

BACKGROUND

COVID-19 has the most impact on people with comorbidities likely due to a **higher inflammatory state**. **Zinc (Zn)** is known for its substantial involvement in immune response as an **antioxidant and anti-inflammatory** agent. Zn plasma levels' clinical significance at COVID diagnosis is not yet established. We investigated **the effects of Zn deficiency and inflammation on COVID-19 outcomes**.

METHODS

- Plasma Zn levels were collected from patients during the acute phase of a confirmed COVID-19 diagnosis.
- Data was dichotomized into **Zn deficient (Zn<75 µg/dL)** and **Zn sufficient (Zn ≥75 µg/dL)**.
- Soluble tumor necrosis factor alpha receptor II (**sTNF-RII**) and intestinal fatty-acid binding protein (**I-FABP**) were also measured.
- **COVID-19 outcomes** were classified according to the **WHO clinical progression scale,** then stratified into **3 groups** [grp 1= (WHO score 0-4) asymptomatic or mild disease; moderate grp 2= (WHO 5-6); and severe grp 3= (7-10)].
- **Adjusted hazard ratios (AHRs)** and 95% Confidence Intervals (CIs) were computed using **cumulative logit regression** and **adjusted for demographics, BMI, comorbidities, inflammation markers, and lab data.**

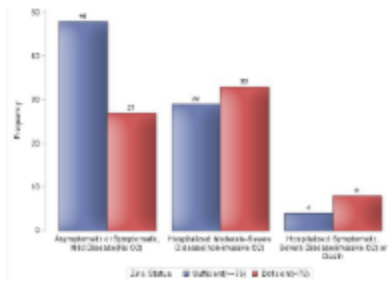


Fig 1. Distribution of Zn status among groups of WHO COVID-19 outcomes

As sTNF-RII levels increase, the risk of severe COVID-19 outcomes rises **two-fold.** Even after adjusting for inflammation, as Zinc levels decrease, the risk of severe COVID-19 outcomes increases.

RESULTS

- **149 patients with a COVID-19 diagnosis were included**.
- The median age (interquartile range [IQR]) was **53 years (38.0, 63.0).**
- **42% were female, 52% were non-white**, and **86% had at least one comorbidity.**
- **54%** of the participants had **sufficient Zn** levels.
- **50%** of patients were classified as **asymptomatic or mild,** 41.5% **moderate**, and **8.5% severe**.
- Patients with **Zn deficiency had a median sTNF-RII of 3027.00** (IQR: 2446.00, 4468.00) **vs. 2965.50** (2431.00, 4358.00) **for patients with Zn sufficiency.**
- In adjusted models, **as Zn levels decreased, the risk of severe COVID-19 outcomes increased** [AHR:0.24 (95% CI: 0.06, 0.93)].
- **As sTNF-RII levels increasesd, but not I-FABP, the risk of severe COVID-19 outcomes rose two-fold** [AHR: 2.17 (95% CI: 1.10, 4.31)].
- **7** out of the 10 Deaths were **zinc deficient**.
- **3** patients had **documented COVID-19 vaccination** before infection.

CONCLUSIONS

- **Zinc deficiency and higher levels of sTNF-RII during acute COVID-19 presentation are independently associated with worse outcomes of COVID-19 outcomes.**
- This suggests a **potential relationship between these 2 variables in COVID-19 progression**.

ADDITIONAL KEY INFORMATION

Author Contact Information:
Christian F. Mouchati, M.D. **cfm71@case.edu**

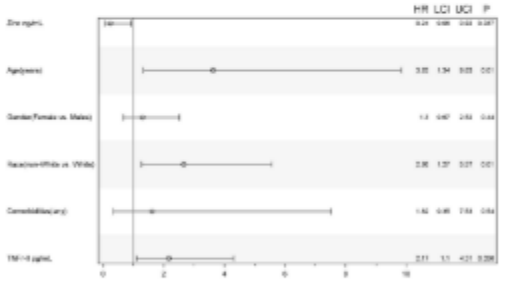


Fig 2. Associations of Zn with COVID-19 disease severity
Adjusted Hazard Ratio (HR), 95% Confidence Interval (CI), and p-value (P)

	Sufficient ≥ 75.0 (n=81)	Deficient <75.0 (n=68)	
Demographics	Median (IQR) / n(%)		p-value
Age (years)	51.00 (36.0, 62.00)	54.5 (41.0, 65.0)	0.09
Female	48 (32.21)	39 (26.17)	0.81
Non-White	31 (20.81)	46 (30.87)	**0.004**
BMI (kg/m2)	33.30 (25.65, 37.38)	31.96 (26.69, 36.44)	0.32

Table 1. Characteristics of COVID-19 positive patients by Zn status

ASSOCIATIONS OF MODERN INITIAL ANTIRETROVIRAL DRUG REGIMENS WITH ALL-CAUSE MORTALITY

00764

CROI 2022

Adam Trickey[1], Lei Zhang[1], Suzanne M. Ingle[1], Antonella Castagna[2], Piotr Cichon[3], Pere Domingo[4], Sophie Grabar[5], Mina Psichogiou[6], Marta Rava[7], Peter Reiss[8], Christopher T. Rentsch[9], Melchor Riera[10], Michael J. Silverberg[11], Caroline Sabin[12], Jonathan A. Sterne[1]. **for the Antiretroviral Therapy Cohort Collaboration (ART-CC) and the UK Collaborative HIV Cohort (UK CHIC)**

[1]University of Bristol, Bristol, United Kingdom, [2]University vita E. Salute, Milan, Italy, [3]Otto-Wagner Hospital, Vienna, Austria, [4]Santa Creu i Sant Pau Hospital, Barcelona, Spain, [5]Sorbonne University, Paris, France, [6]National and Kapodistrian University of Athens, Athens, Greece, [7]Institute of Health Carlos III, Madrid, Spain, [8]Stichting HIV Monitoring, Amsterdam, Netherlands, [9]London School of Hygiene & Tropical Medicine, London, United Kingdom, [10]Hospital Son Espases, Mallorca, Spain, [11]Kaiser Permanente, Oakland, CA, United States, [12]University College London, London, United Kingdom

- **AIM: To compare prognosis for virological failure and all-cause mortality between different INSTI-based and non-INSTI-based ART regimens, using recent multi-country cohort data**

METHODS

- Eligible PWH started ART in Europe and North America between 2013 and 2018.
- We used data from 20 HIV cohort studies (the Antiretroviral Therapy Cohort Collaboration (ART-CC) and UK Collaborative HIV Cohort)
- We studied the most-used third (additional to nucleoside reverse transcriptase inhibitor) antiretroviral drugs during 2013-18: rilpivirine, darunavir, raltegravir, elvitegravir, dolutegravir, and efavirenz

TABLE: Hazard ratios (95% CIs) for mortality for each 3rd drug comparison, using multiple imputation to account for missing data.

Analysis	Mortality	Virologic failure
RPV vs DTG	0.78 (0.55-1.10)	1.31 (1.16-1.48)
DRV vs DTG	0.98 (0.77-1.25)	1.50 (1.35-1.66)
RAL vs DTG	1.49 (1.15-1.94)	1.60 (1.41-1.81)
EVG vs DTG	0.79 (0.60-1.05)	1.39 (1.23-1.56)
EFV vs DTG	0.75 (0.53-1.07)	1.56 (1.38-1.75)
RPV vs EVG	0.93 (0.68-1.28)	0.94 (0.85-1.05)
DRV vs EVG	1.17 (0.92-1.50)	1.08 (0.99-1.19)
RAL vs EVG	1.86 (1.43-2.42)	1.15 (1.02-1.30)
EFV vs EVG	0.87 (0.64-1.18)	1.12 (1.01-1.25)
DRV vs RPV	1.19 (0.91-1.57)	1.15 (1.04-1.27)
RAL vs RPV	1.99 (1.49-2.66)	1.22 (1.08-1.38)
EFV vs RPV	0.93 (0.68-1.27)	1.19 (1.07-1.33)
RAL vs DRV	1.62 (1.33-1.98)	1.06 (0.96-1.18)
EFV vs DRV	0.82 (0.63-1.07)	1.04 (0.94-1.14)
RAL vs EFV	2.12 (1.60-2.81)	1.03 (0.91-1.15)

Rilpivirine (RPV), Darunavir (DRV), Raltegravir (RAL), Elvitegravir (EVG), Dolutegravir (DTG), Efavirenz (EFV).

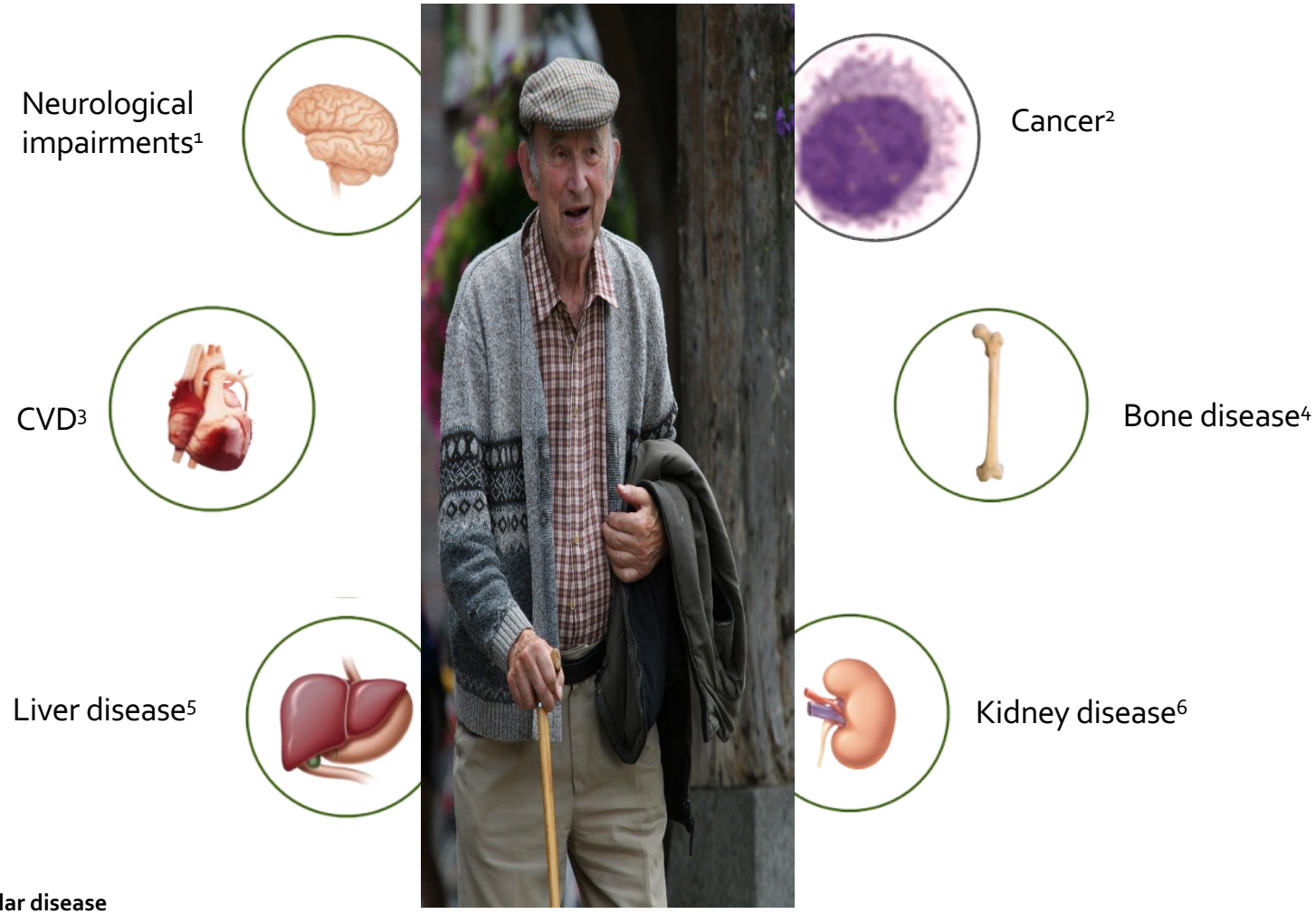
Decline In CD4 Counts And Risk Of Severe Morbidity In PLHIV After Initiating CART

00770

Maria Choufany [1], Laurence Weiss [2], Alain Makinson [3], Helene Roul [1], Jean Michel Livrozet [4], Valérie Pourcher [5], Giovanna Melica [6], Christophe Rioux [7], Jean Paul Viard [2], Esaie Marshall [1], Sophie Grabar [1,8], Dominique Costagliola [1]

- A major CD4 Decline is a rare event, related to global lymphopenia in PLHIV with a controlled viral load under cART
- Older age is associated with the occurrence of a major CD4 decline
- A major CD4 decline is associated with a higher risk of severe morbidity or death

HIV e il tempo



CVD, cardiovascular disease

1. McArthur JC et al. Ann Neurol 2010;67:699–714; 2. Nguyen ML et al. 18th IAC. Vienna, Austria 2010. Abstract WEAB0105;
3. Freiberg MS et al. JAMA Intern Med 2013;173:614–622; 4. Brown TT et al. AIDS 2006;20:2165–2174;
5. Towner WJ et al. JAIDS 2012;60:321–327; 6. Lucas GM et al. Clin Infect Dis 2014;59:e96–e138

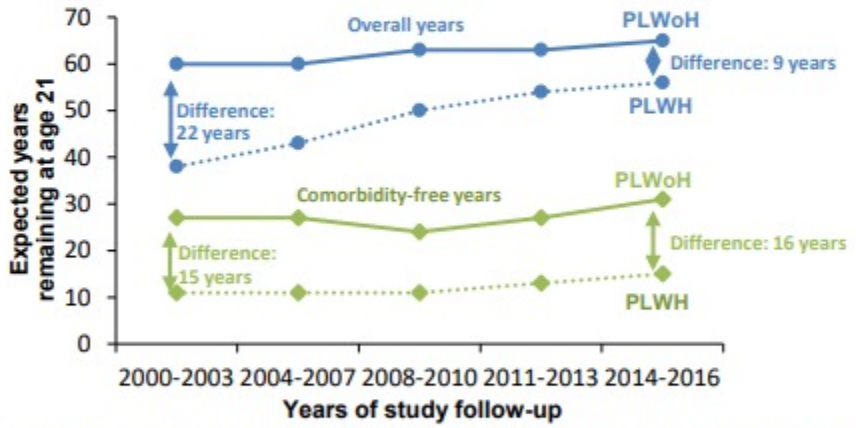
Sick -> disabled -> frail

Glasby J. Health and Social Care, University of Birmingham

Prevention of Comorbidities is an Unmet Need in PLWH

Cohort analysis of comorbidities in PLWH (n = 39,000) and PLWoH (n = 387,767) in US, 2000–2016

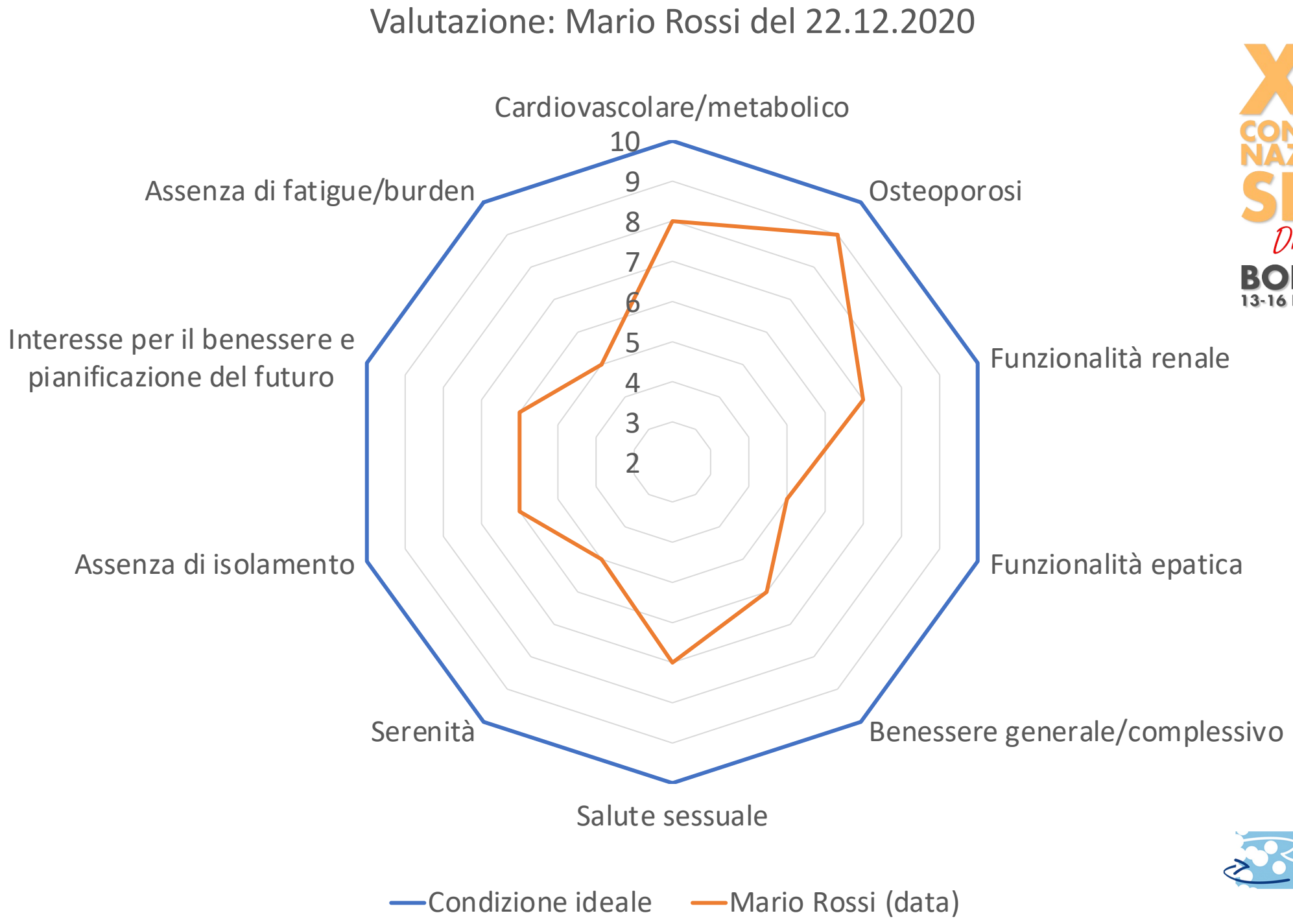
Overall and comorbidity-free life expectancy at age 21



- PLWoH have an expected additional 16 comorbidity-free years versus PLWH
- For each separate comorbidity,* there was a persistent difference in comorbidity-free life expectancy between PLWH and PLWoH
- Initiating ART with a CD4 count >500/µL narrowed the difference in comorbidity-free life expectancy (difference of 9.5 years)

While overall life expectancy has greatly improved for PLWH, individuals still live substantially fewer healthy years than PLWoH

*Chronic liver disease, chronic kidney disease, chronic lung disease, diabetes, cancer, and cardiovascular disease
PLWH, people living with HIV; PLWoH, people living without HIV
Marcus J, et al. *JAMA Netw Open* 2020;3(6):e207954


Valutazione: Mario Rossi del 22.12.2020
Cardiovascolare/metabolico
Osteoporosi
Funzionalità renale
Funzionalità epatica
Benessere generale/complessivo
Salute sessuale
Serenità
Assenza di isolamento
Interesse per il benessere e pianificazione del futuro
Assenza di fatigue/burden
10
9
8
7
6
5
4
3
2
Condizione ideale
Mario Rossi (data)