11

WORKSHOP
NAZIONALE CISAI

TORINO 2023

20 • 21 APRILE

Tollerabilità dei farmaci antinfettivi e co-morbilità associate all'infezione da HIV

Presidenti del Convegno
Paolo Bonfanti, Antonio Di Biagio, Giancarlo Orofino

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11 WORKSHOP NAZIONALE CISAI TORINO 2023
20 • 21 APRILE

Co-morbilità associate all'Infezione da HIV: Top 10 papers (+1) del 2022

Andrea Calcagno
Università di Torino

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Potential Disclosures

I have read and understood ICMJE policy on declaration of interest and I declare that in the past five years

- My institution has received research grants from AbbVie, Gilead Sciences, Bristol Myers Squibb, Janssen-Cilag and ViiV Healthcare

- I received speaker and consultancy honoraria from Gilead Sciences, Insmed, Janssen-Cilag, MSD, Roche, Sobi and ViiV Healthcare

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2022/2023

No CISAI

No party

viruses

MDPI

Article

Reversibility of Central Nervous System Adverse Events in Course of Art

Lucia Taramasso [1,*], Giancarlo Orofino [2], Elena Ricci [3], Barbara Menzaghi [4], Giuseppe Vittorio De Socio [5], Nicola Squillace [6], Giordano Madeddu [7], Francesca Vichi [8], Benedetto Maurizio Celesia [9], Chiara Molteni [10], Federico Conti [11], Filippo Del Puente [12], Eleonora Sarchi [13], Goffredo Angioni [14], Antonio Cascio [15], Carmela Grosso [16], Giustino Parruti [17], Antonio Di Biagio [12] and Paolo Bonfanti [6] on behalf of CISAI Study Group

1 Infectious Disease Clinic, IRCCS Policlinico San Martino Hospital, 16132 Genoa, Italy
2 Unit of Infectious Diseases, "Divisione A", Amedeo di Savoia Hospital, 10149 Torino, Italy; giancarlo.orofino@aslcittaditorino.it
3 Fondazione ASIA Onlus, 20090 Buccinasco, Italy; ed.ricci@libero.it
4 Unit of Infectious Diseases, ASST della Valle Olona, Busto Arsizio Hospital, 21052 Busto Arsizio, Italy; barbara.menzaghi@asst-valleolona.it
5 Clinic of Infectious Diseases, Department of Medicine, Azienda Ospedaliera di Perugia, Santa Maria Hospital, 06129 Perugia, Italy; giuseppedesocio@yahoo.it
6 Infectious Diseases Clinic, San Gerardo Hospital, University of Milano-Bicocca, 20126 Monza, Italy; n.squillace@asst-monza.it (N.S.); paolo.bonfanti@unimib.it (P.B.)
7 Unit of Infectious and Tropical Diseases, Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100 Sassari, Italy; giordano@uniss.it
8 Infectious Diseases Unit 1, Santa Maria Annunziata Hospital, Azienda USL Toscana Centro, 50012 Florence, Italy; francesca.vichi@uslcentro.toscana.it
9 Unit of Infectious Diseases, University of Catania, ARNAS Garibaldi, 95123 Catania, Italy; bmcelesia@tin.it
10 Infectious Diseases Unit, Ospedale A. Manzoni, 23900 Lecco, Italy; c.molteni@asst-lecco.it
11 Infectious Diseases Unit, Department of Biomedical and Clinical Sciences "Luigi Sacco", Università Degli Studi di Milano, 20122 Milan, Italy; federico.conti@unimi.it
12 Department of Health Sciences, Infectious Disease Clinic, University of Genoa, 16145 Genoa, Italy; fildelp@gmail.com (F.D.P.); antonio.dibiagio@hsanmartino.it (A.D.B.)
13 Infectious Diseases Unit, SS. Antonio e Biagio e Cesare Arrigo Hospital, 15121 Alessandria, Italy; eleonora.sarchi@ospedale.al.it
14 Infectious Diseases Unit, SS Trinità Hospital, 09121 Cagliari, Italy; goffredoangioni@gmail.com
15 Infectious and Tropical Diseases Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, 90133 Palermo, Italy; antonio.cascio03@unipa.it
16 Unit of Infectious Diseases, Cesena Hospital, 47521 Cesena, Italy; c.grosso1@virgilio.it
17 Infectious Diseases Unit, Pescara General Hospital, 66020 Pescara, Italy; parrutig@gmail.com
* Correspondence: taramasso.lucia@gmail.com

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Abstract: The purpose of this study is to evaluate the frequency of central nervous system adverse events (CNS-AE) on dolutegravir (DTG) and non-DTG containing ART, and their reversibility, in the observational prospective SCOLTA cohort. Factors associated with CNS-AE were estimated using a Cox proportional-hazards model. 4939 people living with HIV (PLWH) were enrolled in DTG (n = 1179) and non-DTG (n = 3760) cohorts. Sixty-six SNC-AE leading to ART discontinuation were reported, 39/1179 (3.3%) in DTG and 27/3760 (0.7%) in non-DTG cohort. PLWH naïve to ART, with higher CD4 + T count and with psychiatric disorders were more likely to develop a CNS-AE. The risk was lower in non-DTG than DTG-cohort (aHR 0.33, 95% CI 0.19–0.55, $p < 0.0001$). One-year follow-up was available for 63/66 PLWH with CNS-AE. AE resolution was reported in 35/39 and 23/24 cases in DTG and non-DTG cohorts, respectively. The probability of AE reversibility was not different based on ART class, sex, ethnicity, CDC stage, or baseline psychiatric disorder. At the same time, a lower rate of event resolution was found in PLWH older than 50 years ($p = 0.017$). In conclusion, CNS-AE leading to ART discontinuation was more frequent in DTG than non-DTG treated PLWH. Most CNS-AE resolved after ART switch, similarly in both DTG and non-DTG cohorts.

Keywords: CNS; adverse events; HIV; dolutegravir; reversibility; neurocognitive; psychiatric

A very personal selection…

1

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

Bastian Neesgaard, Lauren Greenberg, Jose M Miró, Katharina Grabmeier-Pfistershammer, Gilles Wandeler, Colette Smith, Stéphane De Wit, Ferdinand Wit, Annegret Pelchen-Matthews, Cristina Mussini, Antonella Castagna, Christian Pradier, Antonella d'Arminio Monforte, Jörg J Vehreschild, Anders Sönnerborg, Alain V Anne, Andrew Carr, Loveleen Bansi-Matharu, Jens D Lundgren, Harmony Garges, Felipe Rogatto, Robert Zangerle, Huldrych F Günthard, Line D Rasmussen, Coca Necsoi, Marc van der Valk, Marianna Menozzi, Camilla Muccini, Lars Peters, Amanda Mocroft, Lene Ryom

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See Comment page e451

CHIP, Centre of Excellence for Health, Immunity, and Infections, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (B Neesgaard MD PhD, L Greenberg PhD, Prof J D Lundgren DMSc, L Peters DMSc, Prof A Mocroft PhD, L Ryom DMSc); Infectious Diseases Service, Hospital Clinic–IDIBAPS University of Barcelona, Barcelona, Spain (Prof J M Miró PhD); Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain (Prof J M Miró); Austrian HIV Cohort Study (AHIVCOS), Medizinische Universität Vienna, Vienna, Austria (K Grabmeier-Pfistershammer MD); Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland (Prof G Wandeler MD); The Royal Free HIV Cohort Study, Royal Free Hospital, University College London, London, UK (C Smith PhD); CHU Saint-Pierre, Centre de Recherche en Maladies Infectieuses a.s.b.l., Brussels, Belgium (Prof S De Wit PhD, C Necsoi MD); AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, Stichting HIV Monitoring, Amsterdam, Netherlands (F Wit PhD, Prof M van der Valk PhD); Centre for Clinical Research, Epidemiology, Modelling and

Summary

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

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

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

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

Funding The CHU St Pierre Brussels HIV Cohort, The Austrian HIV Cohort Study, The Australian HIV Observational Database, The AIDS Therapy Evaluation in the Netherlands National Observational HIV cohort, The EuroSIDA cohort, The Frankfurt HIV Cohort Study, The Georgian National AIDS Health Information System, The Nice HIV Cohort, The ICONA Foundation, The Modena HIV Cohort, The PISCIS Cohort Study, The Swiss HIV Cohort Study, The Swedish InfCare HIV Cohort, The Royal Free HIV Cohort Study, The San Raffaele Scientific Institute, The University Hospital Bonn HIV Cohort and The University of Cologne HIV Cohorts, ViiV Healthcare, and Gilead Sciences.

INSTI use and cardiovascular disease

- 29340 INSTI-naïve PLWH
- Median follow-up 6.16 years 748 (2.5%) individuals had a cardiovascular disease → 4.67 events (95% CI 4.34-5.01)per 1000 person-years of follow-up
  - 299 (40%) were myocardial infarctions, 228 (30%) were strokes. and 221 (30%) were invasive cardiovascular procedures
- Higher prevalence of traditional risk factors and older age (higher CVR scores)
- 8.46 per 1000 person-years in the first 6 months of INSTI use (then progressively decreasing, back to BL after 24 weeks)
  - even after adjustment the risk was higher in the first 6 months (aIRR 1.85)

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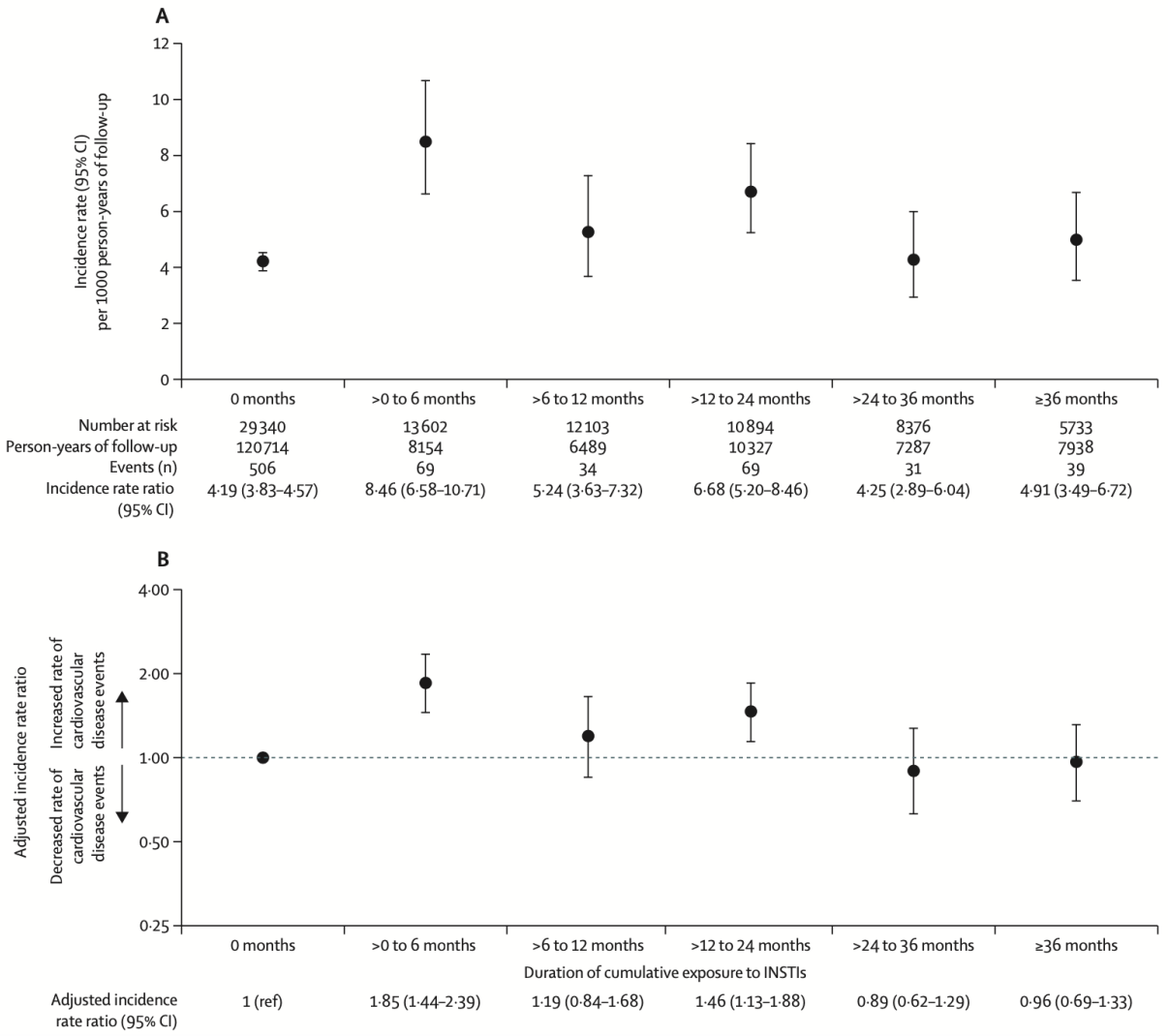
INSTI use and cardiovascular disease



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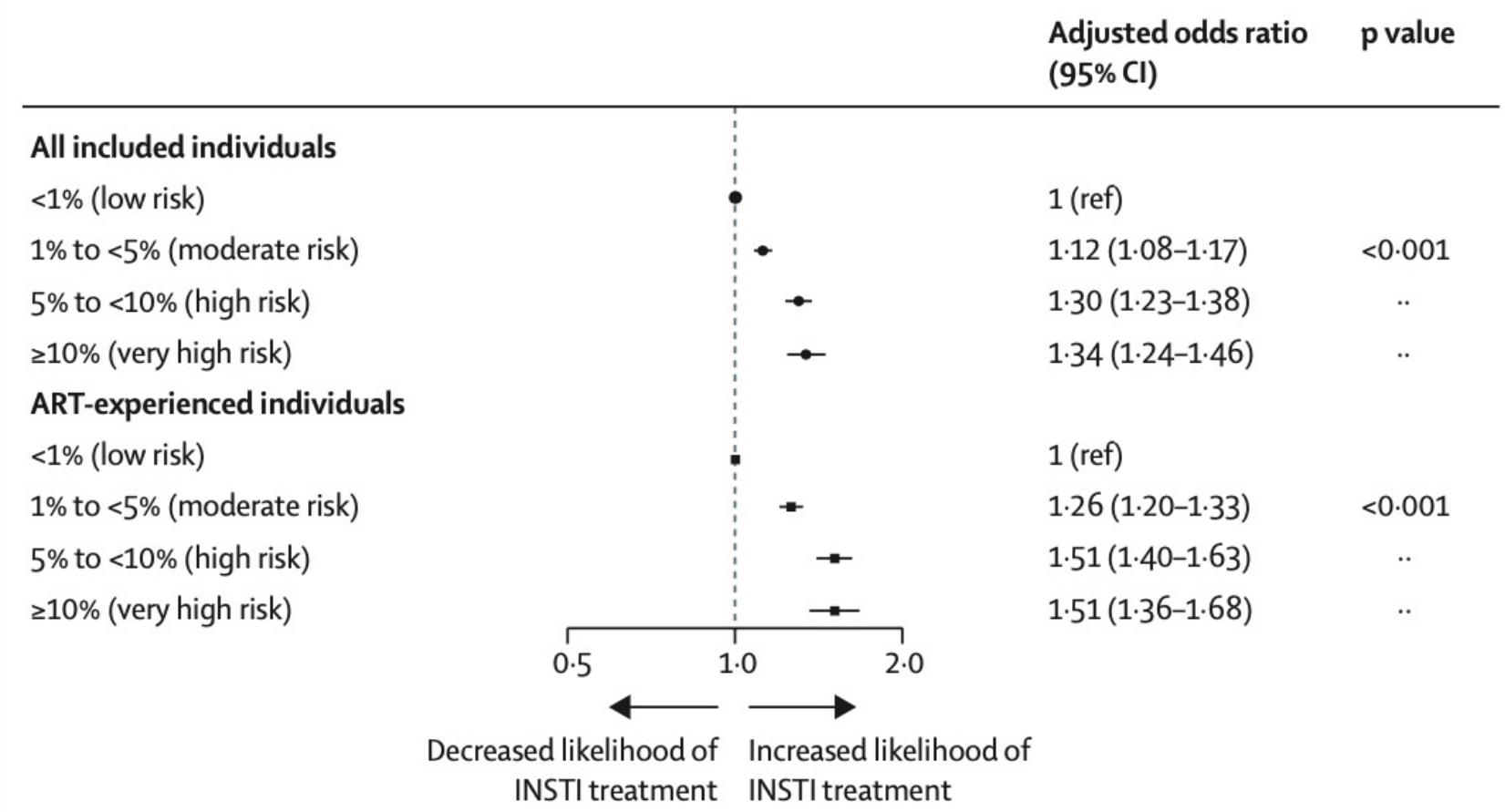
INSTI use and cardiovascular disease



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INSTI use and cardiovascular disease

No statistical power for adjusted analysis for each event of the composite endpoint

34 (15%) of 228 strokes were haemorragic

	0 months of exposure		>0 to 6 months of exposure		>6 to 12 months of exposure		>12 to 24 months of exposure		>24 to 36 months of exposure		>36 months of exposure		p values
	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	
Primary model (n=29 340)*	1 (ref)	506 (120 714)	1·85 (1·44–2·39)	69 (8154)	1·19 (0·84–1·68)	34 (6489)	1·46 (1·13–1·88)	69 (10 327)	0·89 (0·62–1·29)	31 (7287)	0·96 (0·69–1·33)	39 (7938)	<0·0001
Model with time-updated factors on the potential causal pathway (n=29 340)†	1 (ref)	506 (120 714)	1·92 (1·47–2·52)	69 (8154)	1·09 (0·74–1·61)	34 (6489)	1·27 (0·95–1·70)	69 (10 327)	0·81 (0·54–1·22)	31 (7287)	0·87 (0·61–1·26)	39 (7938)	<0·0001
Model with time-updated factors on the potential causal pathway and platelet count (n=29 340)‡	1 (ref)	506 (120 714)	1·93 (1·47–2·52)	69 (8154)	1·09 (0·74–1·61)	34 (6489)	1·27 (0·95–1·70)	69 (10 327)	0·82 (0·54–1·23)	31 (7287)	0·88 (0·61–1·27)	39 (7938)	<0·0001
Model only adjusted for estimated D:A:D 5-year cardiovascular disease risk score (n=29 340)§	1 (ref)	506 (120 714)	2·07 (1·61–2·66)	69 (8154)	1·29 (0·91–1·83)	34 (6489)	1·61 (1·25–2·07)	69 (10 327)	1·00 (0·70–1·45)	31 (7287)	1·11 (0·80–1·53)	39 (7938)	<0·0001
Excluding individuals with previous cardiovascular disease events at baseline (n=28 674)¶	1 (ref)	445 (118 141)	1·83 (1·39–2·41)	60 (7976)	1·12 (0·77–1·63)	29 (6366)	1·36 (1·03–1·80)	58 (10 111)	0·86 (0·58–1·28)	27 (7141)	0·97 (0·69–1·38)	35 (7731)	0·0002
Excluding invasive cardiovascular procedures from the composite cardiovascular disease endpoint (n=29 340)‖	1 (ref)	353 (120 714)	1·77 (1·30–2·41)	47 (8154)	1·13 (0·74–1·73)	23 (6489)	1·55 (1·15–2·08)	52 (10 327)	0·73 (0·45–1·17)	18 (7287)	0·93 (0·63–1·38)	27 (7938)	0·0003
Including only individuals who switched or initiated a new ART regimen after Jan 1, 2012 (n=20 782)**	1 (ref)	118 (34 081)	1·76 (1·31–2·37)	73 (8609)	1·18 (0·82–1·71)	38 (6863)	1·41 (1·05–1·89)	74 (10 922)	0·98 (0·68–1·43)	37 (7730)	1·03 (0·72–1·46)	44 (8412)	0·0023
Including only centrally adjudicated cardiovascular disease events (n=21 188)††	1 (ref)	145 (40 886)	1·37 (0·89–2·12)	26 (4121)	1·30 (0·82–2·06)	22 (3744)	1·33 (0·93–1·90)	48 (7149)	0·93 (0·61–1·42)	27 (6006)	0·88 (0·59–1·31)	34 (7533)	0·22

aIRR=adjusted incidence rate ratio. BMI=body-mass index. D:A:D=Data Collection on Adverse events of Anti-HIV Drugs. INSTI=integrase strand-transfer inhibitor. *Adjusted for age, sex, race, geographical region, BMI, HIV acquisition risk, CD4 cell count, hypertension, diabetes, previous AIDS-defining conditions, previous cardiovascular disease event, chronic kidney disease, and dyslipidaemia, all fixed at baseline. Additionally, smoking and antiretroviral drugs previously associated with cardiovascular disease were included in the model as time-updated variables. †Adjusted as in primary model, with BMI, hypertension, diabetes, dyslipidaemia, chronic kidney disease, and CD4 cell count fitted as time-updated variables. ‡Adjusted as in primary model, with BMI, hypertension, diabetes, dyslipidaemia, chronic kidney disease, and CD4 cell count fitted as time-updated variables, and also time-updated platelet count. §Model adjusted only for D:A:D 5-year cardiovascular disease risk score at baseline. ¶Adjusted as in primary model, excluding individuals with previous cardiovascular disease event at baseline. ‖Adjusted as in primary model, excluding invasive cardiovascular procedures from the composite cardiovascular disease outcome. **Adjusted as in primary model, including only individuals who switched or initiated a new ART regimen after the RESPOND baseline, Jan 1, 2012. ††Adjusted as in primary model, including only centrally validated cardiovascular events; however, because the median time of cardiovascular disease event was before the validation period, the model included a substantially lower number of events (302 [40%] of 748 events were validated, of which 145 were in the no exposure group and 157 were in the exposure group) and had limited statistical power.

Table 2: **Adjusted incidence rate ratio of the cardiovascular disease composite endpoint by cumulative exposure to INSTIs, compared with no INSTI exposure, overall and in exploratory and sensitivity analyses**

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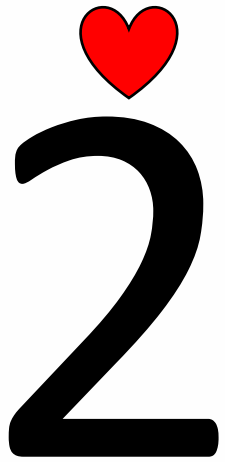

JAMA Cardiology | Original Investigation

Performance of Cardiovascular Risk Prediction Models Among People Living With HIV
A Systematic Review and Meta-analysis

Cullen Soares, MD; Michael Kwok, MSc; Kent-Andrew Boucher, MD; Mohammed Haji, MD; Justin B. Echouffo-Tcheugui, MD, PhD; Christopher T. Longenecker, MD; Gerald S. Bloomfield, MD, MPH; David Ross, MD, PhD; Eric Jutkowtiz, PhD; Jennifer L. Sullivan, PhD; James L. Rudolph, MD, SM; Wen-Chih Wu, MD, MPH; Sebhat Erqou, MD, PhD

IMPORTANCE Extant data on the performance of cardiovascular disease (CVD) risk score models in people living with HIV have not been synthesized.

OBJECTIVE To synthesize available data on the performance of the various CVD risk scores in people living with HIV.

DATA SOURCES PubMed and Embase were searched from inception through January 31, 2021.

STUDY SELECTION Selected studies (1) were chosen based on cohort design, (2) included adults with a diagnosis of HIV, (3) assessed CVD outcomes, and (4) had available data on a minimum of 1 CVD risk score.

DATA EXTRACTION AND SYNTHESIS Relevant data related to study characteristics, CVD outcome, and risk prediction models were extracted in duplicate. Measures of calibration and discrimination are presented in tables and qualitatively summarized. Additionally, where possible, estimates of discrimination and calibration measures were combined and stratified by type of risk model.

MAIN OUTCOMES AND MEASURES Measures of calibration and discrimination.

RESULTS Nine unique observational studies involving 75 304 people (weighted average age, 42 years; 59 490 male individuals [79%]) living with HIV were included. In the studies reporting these data, 86% were receiving antiretroviral therapy and had a weighted average CD4+ count of 449 cells/μL. Included in the study were current smokers (50%), patients with diabetes (5%), and patients with hypertension (25%). Ten risk prediction scores (6 in the general population and 4 in the HIV-specific population) were analyzed. Most risk scores had a moderate performance in discrimination (C statistic: 0.7-0.8), without a significant difference in performance between the risk scores of the general and HIV-specific populations. One of the HIV-specific risk models (Data Collection on Adverse Effects of Anti-HIV Drugs Cohort 2016) and 2 of the general population risk models (Framingham Risk Score [FRS] and Pooled Cohort Equation [PCE] 10 year) had the highest performance in discrimination. In general, models tended to underpredict CVD risk, except for FRS and PCE 10-year scores, which were better calibrated. There was substantial heterogeneity across the studies, with only a few studies contributing data for each risk score.

CONCLUSIONS AND RELEVANCE Results of this systematic review and meta-analysis suggest that general population and HIV-specific CVD risk models had comparable, moderate discrimination ability in people living with HIV, with a general tendency to underpredict risk. These results reinforce the current recommendations provided by the American College of Cardiology/American Heart Association guidelines to consider HIV as a risk-enhancing factor when estimating CVD risk.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sebhat Erqou, MD, PhD, Division of Cardiology, Providence VA Medical Center, 830 Chalkstone Ave, Providence, RI 02908 (sebhaterqou@gmail.com).

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Performance of Cardiovascular Risk Prediction Models Among People Living With HIV - A Systematic Review and Meta-analysis

- Nine unique observational studies involving 75 304 PLWH
- In the studies reporting these data, 86% were receiving antiretroviral therapy and had a weighted average CD4+ count of 449 cells/µL. Included in the study were current smokers (50%), patients with diabetes (5%), and patients with hypertension (25%).
- Ten risk prediction scores (6 in the general population and 4 in the HIV-specific population) were analyzed.
- Most risk scores had a moderate performance in discrimination (C statistic: 0.7-0.8), without a significant difference in performance between the risk scores of the general and HIV-specific populations.
- One of the HIV-specific risk models (Data Collection on Adverse Effects of Anti-HIV Drugs Cohort 2016) and 2 of the general population risk models (Framingham Risk Score [FRS] and Pooled Cohort Equation [PCE] 10 year) had the highest performance in discrimination.
- **In general, models tended to underpredict CVD risk, except for FRS and PCE 10-year scores, which were better calibrated.**

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Performance of Cardiovascular Risk Prediction Models Among People Living With HIV - A Systematic Review and Meta-analysis

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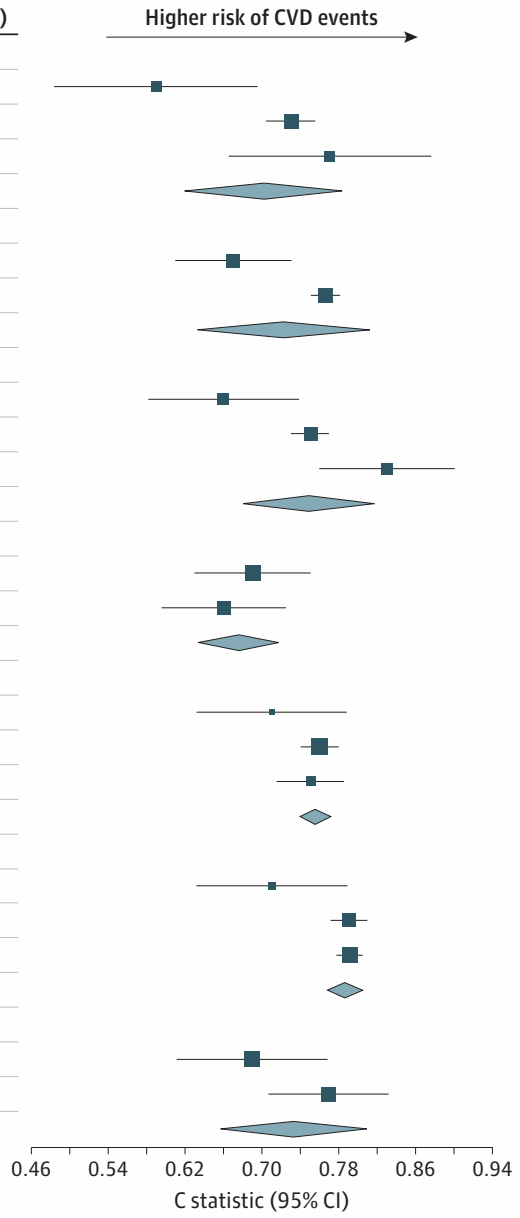
Figure 1. Pooled Analysis of Discrimination Measures (Area Under Operator Curves) Reported by Individual Studies for 4 Cardiovascular Disease (CVD) Risk Prediction Models

Study	Cases, No.	C statistic (95% CI)
SCORE (10 y)		
Thompson-Paul et al,[2] 2016	18	0.59 (0.48-0.70)
van Zoest et al,[11] 2019	1138	0.73 (0.70-0.76)
DeSocio et al,[9] 2017	9	0.77 (0.66-0.88)
Heterogeneity: I^2 = 72%; 95% CI, 5%-92%; P = .03		0.70 (0.62-0.79)
FRS (5 y)		
Triant et al,[1] 2018	78	0.67 (0.61-0.73)
Friis-Møller et al,[5] 2016	1010	0.77 (0.75-0.78)
Heterogeneity: I^2 = 89%; 95% CI, 58%-97%; P = .003		0.72 (0.63-0.82)
FRS (10 y)		
Thompson-Paul et al,[2] 2016	199	0.66 (0.58-0.74)
van Zoest et al,[11] 2019	1393	0.75 (0.73-0.77)
DeSocio et al,[9] 2017	34	0.83 (0.76-0.90)
Heterogeneity: I^2 = 80%; 95% CI, 37%-94%; P = .007		0.75 (0.68-0.82)
PCE (5 y)		
Thompson-Paul et al,[2] 2016	96	0.69 (0.63-0.75)
Triant et al,[1] 2018	78	0.66 (0.60-0.72)
Heterogeneity: I^2 = 0%; P = .51		0.68 (0.63-0.72)
PCE (10 y)		
Thompson-Paul et al,[2] 2016	151	0.71 (0.63-0.79)
van Zoest et al,[11] 2019	955	0.76 (0.74-0.78)
Feinstein et al,[3] 2017	614	0.75 (0.71-0.79)
Heterogeneity: I^2 = 0%; P = .45		0.76 (0.74-0.77)
D:A:D 2016 (5 y, full model)		
Thompson-Paul et al,[2] 2016	141	0.71 (0.63-0.79)
van Zoest et al,[11] 2019	478	0.79 (0.77-0.81)
Friis-Møller et al,[5] 2016	1010	0.79 (0.78-0.80)
Heterogeneity: I^2 = 49.9%; 95% CI, 0-85%; P = .14		0.79 (0.77-0.81)
D:A:D 2010 (5 y)		
Thompson-Paul et al,[2] 2016	141	0.69 (0.61-0.77)
Friis-Møller et al,[5] 2016	663	0.77 (0.71-0.83)
Heterogeneity: I^2 = 58.0%; 95% CI, 0-90%; P = .12		0.73 (0.66-0.81)



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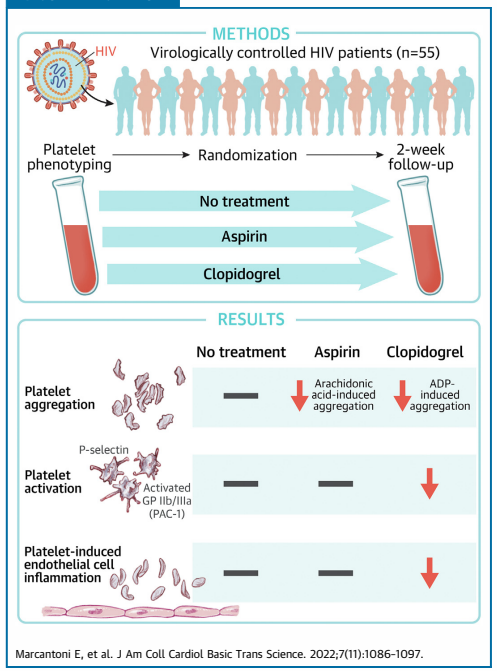
ORIGINAL RESEARCH - CLINICAL

Antiplatelet Effects of Clopidogrel Vs Aspirin in Virologically Controlled HIV

A Randomized Controlled Trial

Emanuela Marcantoni, PhD,[a,*] Michael S. Garshick, MD, MS,[a,b,*] Tamar Schwartz, BA,[a] Nicole Ratnapala, MS,[c] Matthew Cambria, BA,[d] Rebecca Dann, MS,[e] Meagan O'Brien, MD,[f] Adriana Heguy, PhD,[g] Jeffrey S. Berger, MD, MS[a,b,h,i]

VISUAL ABSTRACT



Marcantoni E, et al. J Am Coll Cardiol Basic Trans Science. 2022;7(11):1086-1097.

HIGHLIGHTS

- **In treated HIV, cardiovascular disease is a leading cause of morbidity and mortality, the prevention of which is not fully known.**
- **Activated platelets are causal in atherosclerotic cardiovascular disease, and platelets in HIV exhibit heightened activity.**
- **In this study, clopidogrel, as opposed to aspirin, reduced platelet activation, and platelet-induced endothelial inflammation in persons with HIV.**
- **The use of clopidogrel for the primary prevention of cardiovascular disease in HIV should be evaluated in more extensive clinical trials.**

From the [a]Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, New York, USA; [b]Center for the Prevention of Cardiovascular Disease, Department of Medicine, New York University School of Medicine, New York, New York, USA; [c]Dartmouth Geisel School of Medicine, Hanover, New Hampshire, USA; [d]Division of Vascular and Endovascular Surgery, Department of Surgery, New York University School of Medicine, New York, New York, USA; [e]New York Medical College, Valhalla, New York, USA; [f]Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA; [g]Genome Technology Center, New York University School of Medicine, New York, New York, USA; [h]Division of Hematology, Department of

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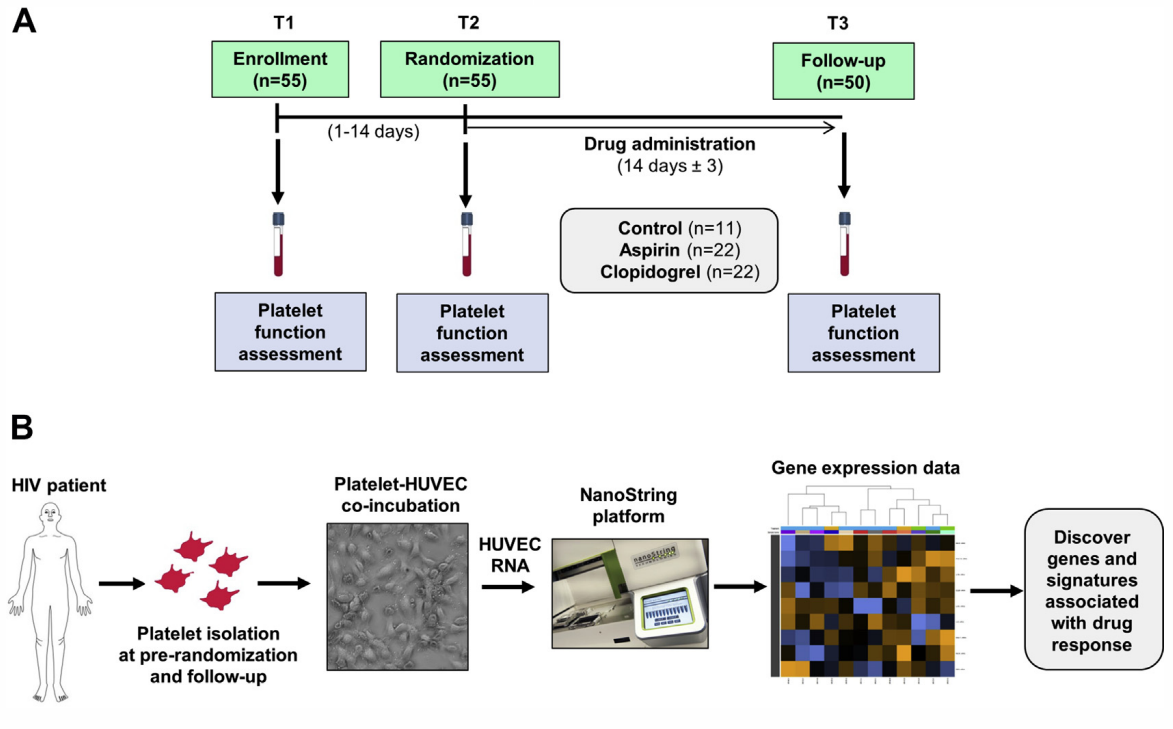
Antiplatelet Effects of Clopidogrel Vs Aspirin in Virologically Controlled HIV A Randomized Controlled Trial

FIGURE 1 Clinical Trial and Experimental Design



Schematic of clinical trial. **(A)** Study site visit and platelet phenotype assessment at (T1) enrollment, (T2) randomization, and (T3) follow-up at day 14. **(B)** Freshly isolated platelets (n = 2 per group) coincubated on HUVECs for 2 hours at T2 and T3. Isolated mRNA from HUVECS underwent NanoString transcriptomic analysis (n = 594), whereas a separate validation cohort (n = 11 to 14 per group) underwent platelet-HUVEC coincubation experiments with subsequent quantitative polymerase chain reaction (of HUVEC transcriptome expression) at study end (T3). HIV = human Immunodeficiency virus; HUVEC = human umbilical vein endothelial cell.

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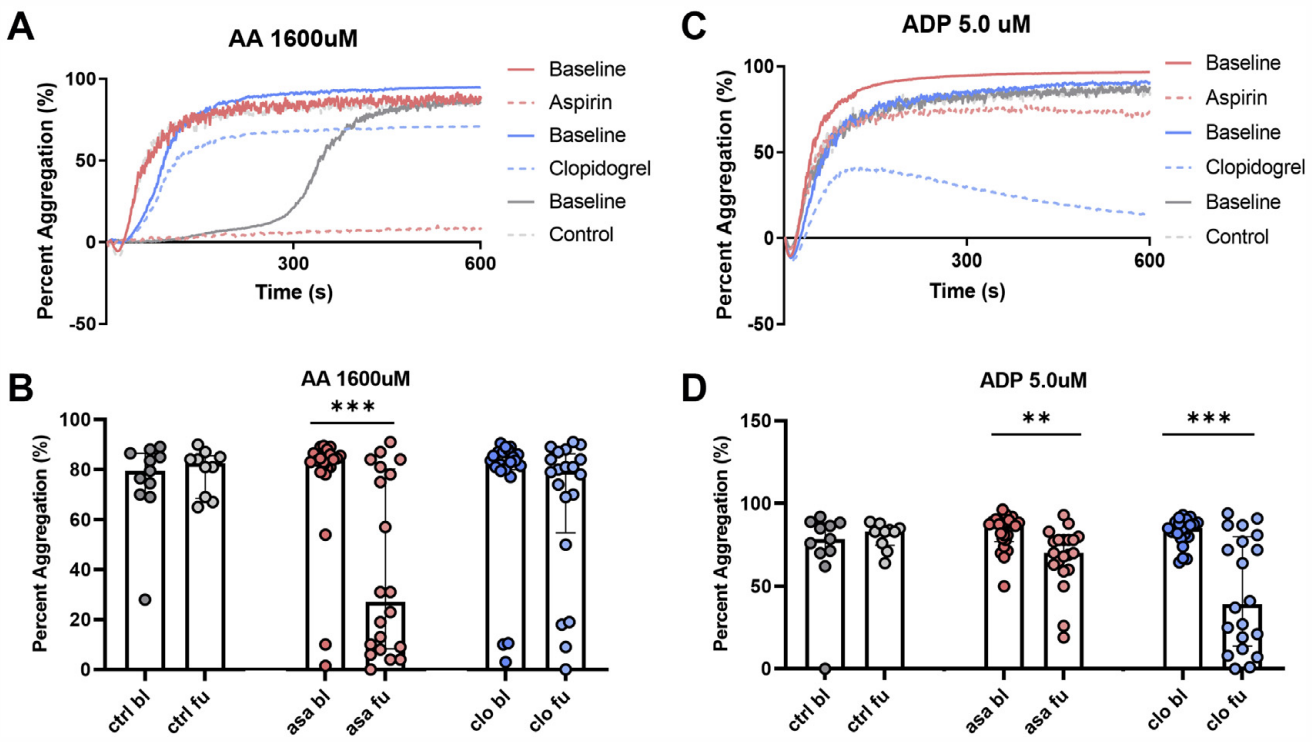
FIGURE 2 AA- and ADP-Induced Platelet Aggregation Are Inhibited After Aspirin and Clopidogrel Treatment



Percent platelet aggregation using light transmission aggregometry. **(A)** Representation of platelet aggregation studies and **(B)** percent aggregation at 300 seconds in response to 1,600 μmol/L arachidonic acid by study assignment. **(C)** Representation of platelet aggregation studies and **(D)** percent aggregation at 300 seconds in response to 5.0 μmol/L of ADP by study assignment. n = ~22 per group (aspirin/clopidogrel), n = ~11 per group (control); $^{**}P < 0.01$, $^{***}P < 0.001$ by Wilcoxon signed-rank test. Bar graphs indicate median with IQR. AA = arachidonic acid; ADP = adenosine diphosphate; asa = aspirin; bl = baseline; clo = clopidogrel; Ctrl = control; fu = follow-up.

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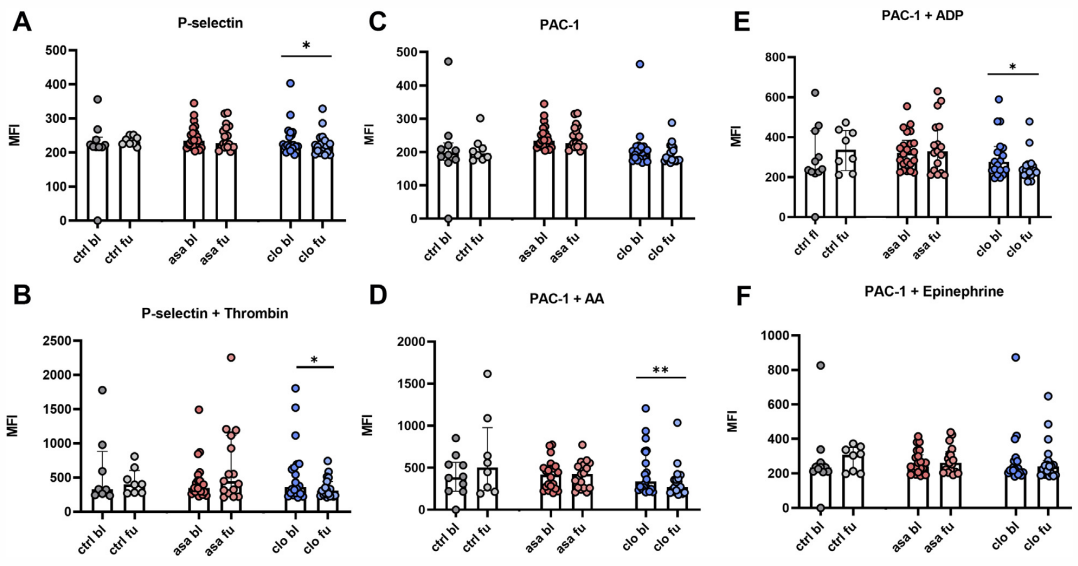
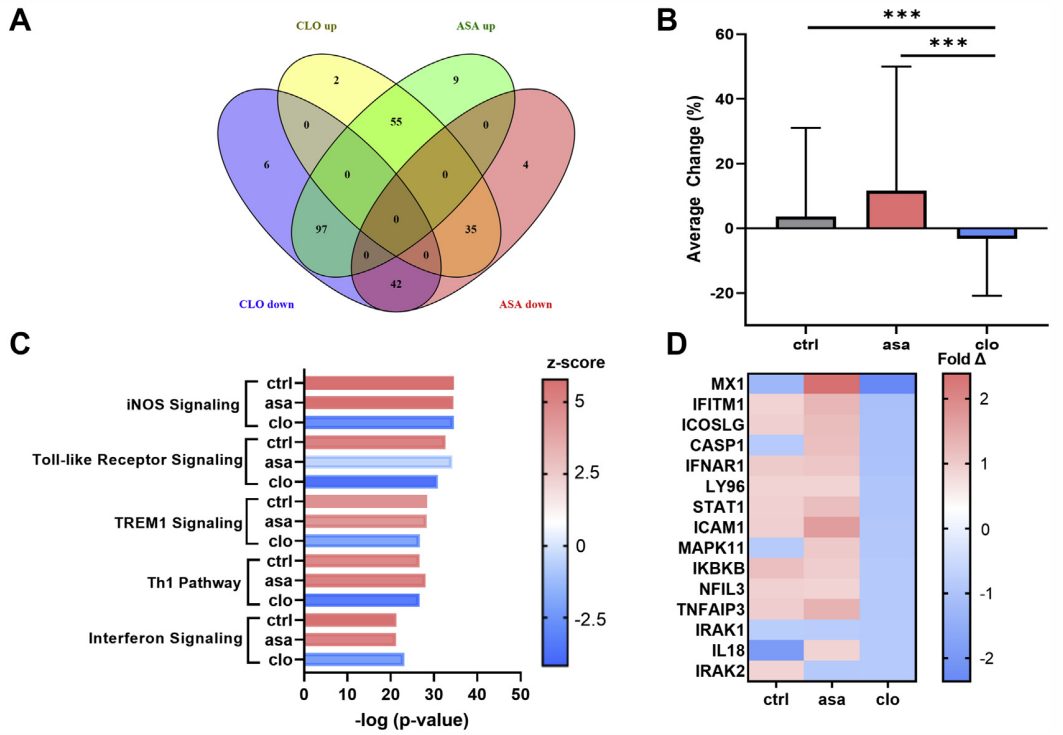
FIGURE 3 Platelet P-Selectin and PAC-1 Expression Is Reduced After Aspirin and Clopidogrel Treatment



Platelet flow-cytometry (expressed as mean fluorescence units [MFI]). Resting **(A)** and **(B)** thrombin (0.05 U/mL) stimulated platelet p-selectin ($CD62p^+$, $CD42b^+$) expression in each treatment group. Resting **(C)**, arachidonic acid (**D**, 0.60 μmol/L), ADP (**E**, 0.1 μmol/L), and epinephrine (**F**, 0.4 μmol/L) stimulated PAC-1 ($CD42b^+$ $PAC\text{-}1^+$) expression. All stimulated treatments occurred over 5 minutes. $^{**}P < 0.01$, $^{***}P < 0.001$ by Wilcoxon signed rank test. Bar graphs indicate median with IQR. Abbreviations as in Figure 2.

FIGURE 4 Platelet-Treated Composite Endothelial Transcript Expression Is Reduced After Clopidogrel



Freshly isolated platelets at study randomization and follow-up (n = 2 per study assignment group) were coincubated on human umbilical vein endothelial cells (HUVECS) × 2 hours and the HUVEC transcriptome assessed using the NanoString immunology panel (594 genes). **(A)** Venn diagram displacing directionality and change in all measurable HUVEC transcripts by study assignment (~246 genes). **(B)** Average change, expressed as percentage, in the composite HUVEC transcriptome by study assignment. **(C)** Top 5 down-regulated canonical pathways in the clopidogrel treatment arm vs aspirin and control arms (by Ingenuity Pathway Analysis). **(D)** Normalized (to control) fold change in HUVEC transcripts obtained from **C** by study assignment. $^{***}P < 0.001$ (analysis of covariance and Student's *t*-test for posttreatment scores). iNOS = inducible nitric oxide synthase; other abbreviations as in Figure 2.

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BMC Geriatrics

RESEARCH Open Access

Effects of frailty, geriatric syndromes, and comorbidity on mortality and quality of life in older adults with HIV

Fátima Brañas[1*†], Miguel Torralba[2], Antonio Antela[3], Jorge Vergas[4], Margarita Ramírez[5], Pablo Ryan[6], Fernando Dronda[7], María José Galindo[8], Isabel Machuca[9], María Jesús Bustinduy[10], Alfonso Cabello[11], María Luisa Montes[12], Matilde Sánchez-Conde[7†] and FUNCFRAIL study group

Abstract

Background: To understand the effects of frailty, geriatric syndromes, and comorbidity on quality of life and mortality in older adults with HIV (OAWH).

Methods: Cross-sectional study of the FUNCFRAIL multicenter cohort. The setting was outpatient HIV-Clinic. OAWH, 50 year or over were included. We recorded sociodemographic data, HIV infection-related data, comorbidity, frailty, geriatric syndromes (depression, cognitive impairment, falls and malnutrition), quality of life (QOL) and the estimated risk of all-cause 5-year mortality by VACS Index. Association of frailty with geriatric syndromes and comorbidity was evaluated using the Cochran-Mantel-Haenszel test.

Results: Seven hundred ninety six patients were included. 24.7% were women, mean age was 58.2 (6.3). 14.7% were 65 or over. 517 (65%) patients had ≥3 comorbidities, ≥ 1 geriatric syndrome and/or frailty. There were significant differences in the estimated risk of mortality [(frailty 10.8%) vs. (≥ 3 comorbidities 8.2%) vs. (≥ 1 geriatric syndrome 8.2%) vs. (nothing 6.2%); $p = 0.01$] and in the prevalence of fair or poor QOL [(frailty 71.7%) vs. (≥ 3 comorbidities 52%) vs. (≥ 1 geriatric syndrome 58.4%) vs. (nothing 51%); $p = 0.01$]. Cognitive impairment was significantly associated to mortality (8.7% vs. 6.2%; $p = 0.02$) and depression to poor QOL [76.5% vs. 50%; $p = 0.01$].

Conclusions: Frailty, geriatric syndromes, and comorbidity had negative effects on mortality and QOL, but frailty had the greatest negative effect out of the three factors. Our results should be a wake-up call to standardize the screening for frailty and geriatric syndromes in OAWH in the clinical practice.

Trial registration: NCT03558438.

Keywords: HIV, Frailty, Geriatric syndromes, Mortality, Quality of life

Background

Older adults comprise more than half of the people living with HIV, especially in high-income countries, and this proportion is estimated to globally increase so that 23% of older persons with HIV will be 65 or older by 2030 [1, 2]. Even if the targets for reducing HIV diagnoses were met, the number of people living with HIV would fall but the proportion of older people would increase, as would the median age of people

†Fátima Brañas and Matilde Sánchez-Conde contributed equally to this work.

*Correspondence: fbranas@gmail.com

[1] Geriatrics Department, Hospital Universitario Infanta Leonor, Fundación para la Investigación e Innovación Biomédica H.U Infanta Leonor y H.U. Sureste. Universidad Complutense, Madrid, Spain
Full list of author information is available at the end of the article

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Effects of frailty, geriatric syndromes, and comorbidity on mortality and quality of life in older adults with HIV

- Cross-sectional study of the FUNCFRAIL multicenter cohort (Spain).
  - >50 years
- 696 PLWH
  - 24.7% were women, mean age was 58.2 (6.3). 14.7% were 65 or over.
  - 517 (65%) patients had ≥3 comorbidities, ≥ 1 geriatric syndrome and/or frailty.
- **There were significant differences in the estimated risk of mortality** [(frailty 10.8%) vs. (≥ 3 comorbidities 8.2%) vs. (≥ 1 geriatric syndrome 8.2%) vs. (nothing 6.2%); *p* = 0.01] **and in the prevalence of fair or poor QOL** [(frailty 71.7%) vs. (≥ 3 comorbidities 52%) vs. (≥ 1 geriatric syndrome 58.4%) vs. (nothing 51%); *p* = 0.01].
  - Cognitive impairment was significantly associated to mortality (8.7% vs. 6.2%; *p* = 0.02) and depression to poor QOL [76.5% vs. 50%; p = 0.01].

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Effects of frailty, geriatric syndromes, and comorbidity on mortality and quality of life in older adults with HIV

Frailty (13.5%) and prefrailty (63.3%) in PLWH >70 years in France

Allavena C, AIDS 2023

QOL was evaluated by self-assessment: patients stratified their QOL into one of the following categories: very good, good, fair, or poor.

	Total	Men	Women	*p*
Patients. *N* (%)	796	602 (75.9)	194 (24.1)	
Frailty				
Frailty. *N* (%)	46 (5.8)	35 (5.8)	11 (5.7)	1
Prefrailty. *N* (%)	417 (52.7)	311 (51.6)	106 (54.6)	0.50
Comorbidity				
≥ 3 comorbidities. *N* (%)	306 (38.4)	218 (36.2)	88 (45.4)	0.02
Hypertension. *N* (%)	228 (28.7)	182 (30.2)	46 (23.8)	0.09
Type 2 Diabetes. *N* (%)	107 (13.5)	89 (14.9)	18 (9.3)	0.04
Dyslipidemia. *N* (%)	348 (43.8)	259 (43.2)	89 (45.9)	0.50
Osteoarthritis. *N* (%)	167 (21.2)	102 (17.1)	65 (34)	0.01
Chronic renal failure. *N* (%)	50 (6.3)	40 (6.7)	10 (5.2)	0.60
Cancer. *N* (%)	55 (6.9)	43 (7.2)	12 (6.2)	0.70
History of cancer. *N* (%)	59 (7.4)	34 (5.7)	25 (12.9)	0.01
COPD. *N* (%)	87 (11)	63 (10.5)	24 (12.5)	0.40
Psychiatric disorders. *N* (%)	73 (9.3)	51 (8.6)	22 (11.4)	0.20
Geriatric Syndromes				
≥ 1 geriatric syndrome. *N* (%)	389 (48.9)	272 (45.2)	117 (60.3)	0.01
Falls. *N* (%)	124 (15.6)	81 (13.5)	43 (22.2)	0.01
Depression. *N* (%)	213 (26.8)	153 (25.5)	60 (30.9)	0.10
Cognitive impairment. *N* (%)	96 (12.1)	71 (11.8)	25 (12.9)	0.70
Malnutrition risk. *N* (%)	143 (18.1)	101 (16.9)	42 (21.8)	0.10
Quality of life				
Fair or poor. *N* (%)	(57.7)	337 (55.7)	124 (63.3)	0.06
Mortality				
VACS Index score. Median (p25-p75)	22 (17–29)	18 (12–29)	23 (18–33)	0.01
Estimated risk of all-cause 5-year mortality by VACS Index. Median (p25-p75)	7.8 (5.8–11.3)	6.2 (4.2–11.3)	8.4 (6.2–13.8)	0.01

Frailty and prefrailty defined according to Frailty Phenotype. The GS considered were falls, cognitive impairment, depression, and risk of malnutrition. Cognitive impairment defined as MOCA test score < 20 points. Depression defined as SF-GDS score ≥ 6 points. Falls: at least one fall in the last year. Risk of malnutrition defined as MNA-SF score < 11 points. QOL evaluated by self-assessment and categorized into very good, good, fair, or poor. The Veterans Aging Cohort Study Index is a score created by summing pre-assigned points for age, CD4 count, HIV-1 RNA, hemoglobin, platelets, AST, ALT, creatinine, and viral hepatitis C infection. The higher the score the higher the risk of all-cause mortality. The risk can be estimated using the VACS index calculator (https://www.mdcalc.com/calc/2201/veterans-aging-cohort-study-vacs-1.0-index)

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Cognitive impairment defined as MOCA test score < 20 points

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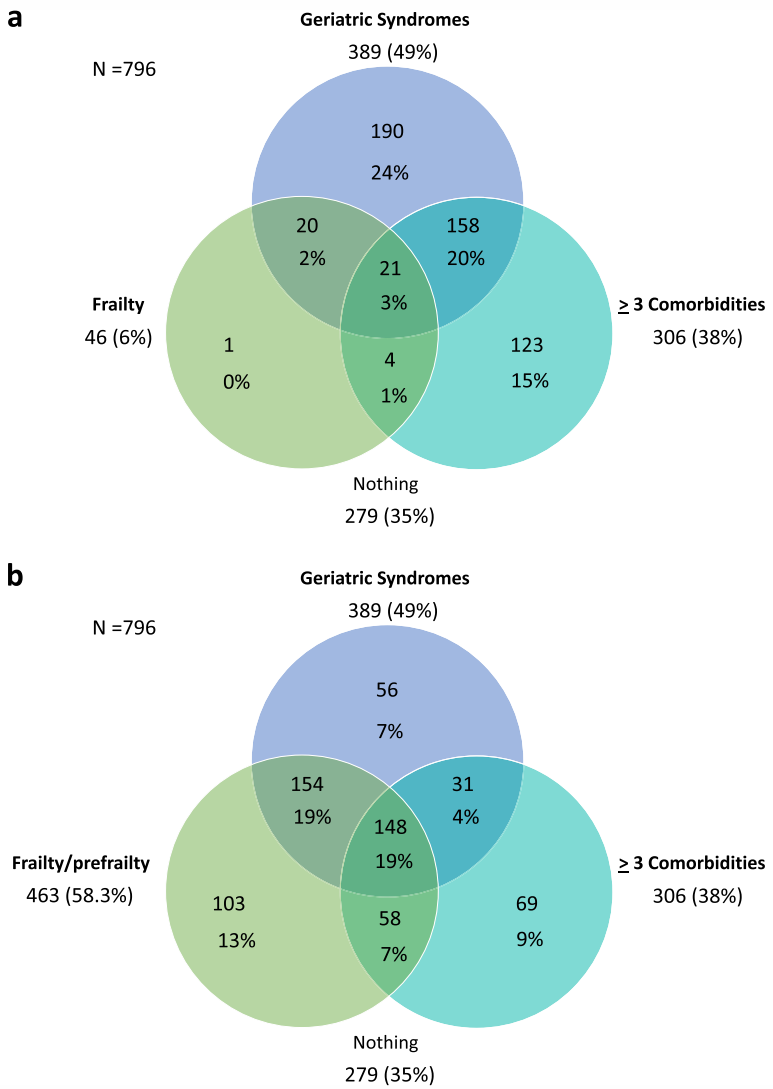

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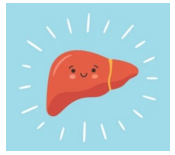

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Clinical Infectious Diseases

MAJOR ARTICLE

Fibroscan-aspartate aminotransferase (FAST) score predicts liver-related outcomes, but not extra-hepatic events, in a multicenter cohort of people with HIV

Giada Sebastiani[1,2], Jovana Milic[3], Dana Kablawi[1], Claudia Gioe'[4], Al Shaima Al Hinai[1], Bertrand Lebouché[2,5], Emmanuel Tsochatzis[6], Jemima Finkel[6], Luz Ramos Ballesteros[1], Agnihotram V. Ramanakumar[7], Sanjay Bhagani[6], Amine Benmassaoud[1], Giovanni Mazzola[8] Antonio Cascio[4,9], Giovanni Guaraldi[3]

[1]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Canada; [2]Chronic Viral Illness Service, Division of Infectious Diseases, Department of Medicine, McGill University Health Centre, Montreal, Canada; [3]Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia, Modena, Italy; [4]Infectious and Tropical Disease Unit, AOU Policlinico "P. Giaccone", Palermo, Italy; [5]Department of Family Medicine, Faculty of Medicine and Health Sciences, McGill University Health Centre, Montreal, Canada; [6]Royal Free London NHS Foundation Trust, London, United Kingdom; [7]Research Institute, McGill University Health Centre, Montreal, Quebec, Canada; [8]Infectious Diseases Unit, Sant'Elia Hospital, Caltanissetta, Italy; [9]Department of Health Promotion Sciences and Mother and Child Care "Giuseppe D'Alessandro", University of Palermo, Palermo, Italy

Background: Nonalcoholic fatty liver disease (NAFLD) is frequent in people with HIV (PWH). The Fibroscan-aspartate aminotransferase (FAST) score was developed to identify patients with nonalcoholic steatohepatitis (NASH) and significant fibrosis. We investigated prevalence of NASH with fibrosis and the value of FAST score in predicting clinical outcomes in PWH.

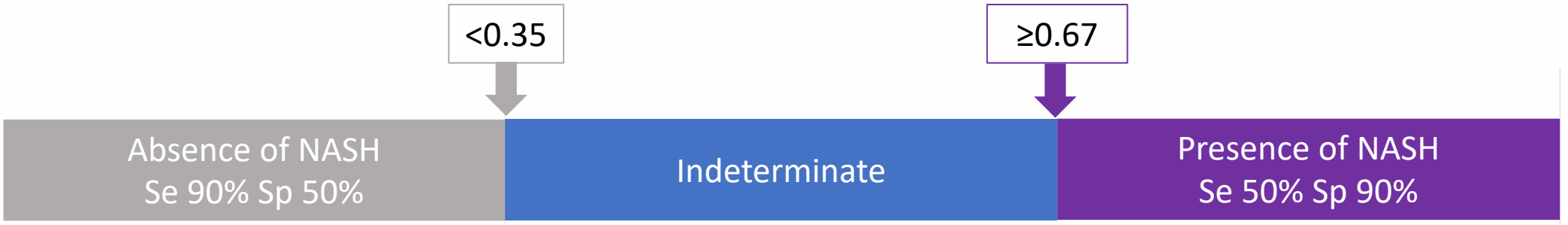
Methods: Transient elastography (Fibroscan) was performed in PWH without viral hepatitis coinfection from four prospective cohorts. We used FAST>0.35 to diagnose NASH with fibrosis.

Corresponding author Dr Giada Sebastiani, MD, Division of Gastroenterology and Hepatology; Chronic Viral Illness Service, Royal Victoria Hospital, McGill University Health Center, 1001 Décarie Blvd., Montreal, QC H4A 3J1, Canada. Email: giada.sebastiani@mcgill.ca

Fibroscan-aspartate aminotransferase (FAST) score predicts liver-related outcomes, but not extra-hepatic events, in a multicenter cohort of people with HIV

- Fibroscan in PLWH without viral hepatitis

$$FAST = \frac{e^{-1.65 + 1.07 \times \ln(LSM) + 2.66*10^{-8} \times CAP^3 - 63.3 \times AST^{-1}}}{1 + e^{-1.65 + 1.07 \times \ln(LSM) + 2.66*10^{-8} \times CAP^3 - 63.3 \times AST^{-1}}}$$



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Fibroscan-aspartate aminotransferase (FAST) score predicts liver-related outcomes, but not extra-hepatic events, in a multicenter cohort of people with HIV

- Fibroscan in PLWH without viral hepatitis (FAST ≥0.35)
- 1472 PLWH → 8% had FAST>0.35.
- On multivariable logistic regression:
  - higher BMI (aOR 1.21)
  - hypertension (aOR 2.24)
  - longer time since HIV diagnosis (aOR 1.82)
  - detectable HIV viral load (aOR 2.22)
- 882 patients were followed for a median of 3.8 years (interquartile range 2.5-4.2). Overall, 2.9% and 11.1% developed liver-related and extra-hepatic outcomes,
- **Incidence of liver-related outcomes was higher in patients with FAST>0.35 (45.1% vs. 5.0%).** On multivariable Cox regression analysis, FAST>0.35 remained an independent predictor of liver-related outcomes (aHR 4.97) but not of extra-hepatic events.

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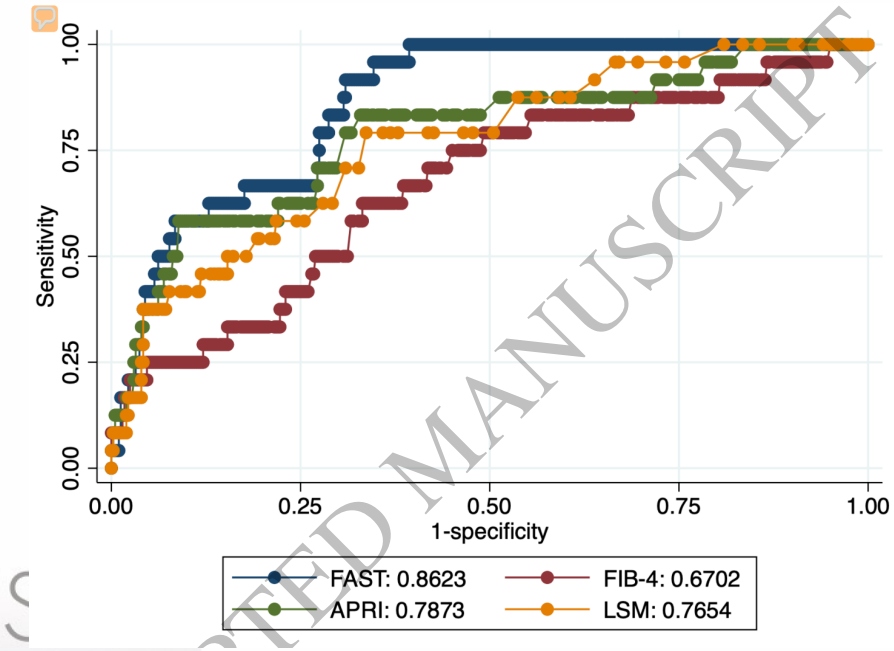
Fibroscan-aspartate aminotransferase (FAST) score predicts liver-related outcomes, but not extra-hepatic events, in a multicenter cohort of people with HIV

Liver-related outcomes

hepatic decompensation, hepatocellular carcinoma, liver transplantation

Figure 1. Flow chart displaying the selection of study participants and the two study cohorts (prevalence and incidence).



Extra-hepatic events

Cardiovascular disease, extra-hepatic cancer and all-cause mortality.

AUROC	
FAST	0.54
APRI	0.54
FIB-4	**0.70**
LSM	0.63

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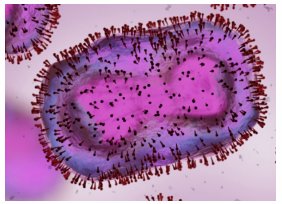

Mpox in people with advanced HIV infection: a global case series

Oriol Mitjà, Andrea Alemany*, Michael Marks*, Jezer I Lezama Mora, Juan Carlos Rodríguez-Aldama, Mayara Secco Torres Silva, Ever Arturo Corral Herrera, Brenda Crabtree-Ramirez, José Luis Blanco, Nicolo Girometti, Valentina Mazzotta, Aniruddha Hazra, Macarena Silva, Juan José Montenegro-Idrogo, Kelly Gebo, Jade Ghosn, María Fernanda Peña Vázquez, Eduardo Matos Prado, Uche Unigwe, Judit Villar-García, Noah Wald-Dickler, Jason Zucker, Roger Paredes, Alexandra Calmy, Laura Waters, Cristina Galvan-Casas, Sharon Walmsley, Chloe M Orkin, on behalf of SHARE-NET writing group*

Summary

Background People living with HIV have accounted for 38–50% of those affected in the 2022 multicountry mpox outbreak. Most reported cases were in people who had high CD4 cell counts and similar outcomes to those without HIV. Emerging data suggest worse clinical outcomes and higher mortality in people with more advanced HIV. We describe the clinical characteristics and outcomes of mpox in a cohort of people with HIV and low CD4 cell counts (CD4 <350 cells per mm³).

Methods A network of clinicians from 19 countries provided data of confirmed mpox cases between May 11, 2022, and Jan 18, 2023, in people with HIV infection. Contributing centres completed deidentified structured case report sheets to include variables of interest relevant to people living with HIV and to capture more severe outcomes. We restricted this series to include only adults older than 18 years living with HIV and with a CD4 cell count of less than 350 cells per mm³ or, in settings where a CD4 count was not always routinely available, an HIV infection clinically classified as US Centers for Disease Control and Prevention stage C. We describe their clinical presentation, complications, and causes of death. Analyses were descriptive.

Findings We included data of 382 cases: 367 cisgender men, four cisgender women, and ten transgender women. The median age of individuals included was 35 (IQR 30–43) years. At mpox diagnosis, 349 (91%) individuals were known to be living with HIV; 228 (65%) of 349 adherent to antiretroviral therapy (ART); 32 (8%) of 382 had a concurrent opportunistic illness. The median CD4 cell count was 211 (IQR 117–291) cells per mm³, with 85 (22%) individuals with CD4 cell counts of less than 100 cells per mm³ and 94 (25%) with 100–200 cells per mm³. Overall, 193 (51%) of 382 had undetectable viral load. Severe complications were more common in people with a CD4 cell count of less than 100 cells per mm³ than in those with more than 300 cells per mm³, including necrotising skin lesions (54% *vs* 7%), lung involvement (29% *vs* 0%) occasionally with nodules, and secondary infections and sepsis (44% *vs* 9%). Overall, 107 (28%) of 382 were hospitalised, of whom 27 (25%) died. All deaths occurred in people with CD4 counts of less than 200 cells per mm³. Among people with CD4 counts of less than 200 cells per mm³, more deaths occurred in those with high HIV viral load. An immune reconstitution inflammatory syndrome to mpox was suspected in 21 (25%) of 85 people initiated or re-initiated on ART, of whom 12 (57%) of 21 died. 62 (16%) of 382 received tecovirimat and seven (2%) received cidofovir or brincidofovir. Three individuals had laboratory confirmation of tecovirimat resistance.

Interpretation A severe necrotising form of mpox in the context of advanced immunosuppression appears to behave like an AIDS-defining condition, with a high prevalence of fulminant dermatological and systemic manifestations and death.

Funding None.

Introduction

Since May, 2022, around 85 000 human mpox (formerly known as monkeypox) infections have been reported in 110 countries, with transmission predominantly through sexual contact among men who have sex with men.[1] The multicountry outbreak was declared a public health emergency of international concern by WHO in July, 2022.[2] People with HIV have been disproportionately affected, accounting for 38–50% of people diagnosed with mpox.[3] Most people living with HIV described in the 2022 case series had HIV viral suppression with median CD4 counts of more than 500 cells per mm³ and had similar clinical presentations, time to monkeypox viral clearance, and outcomes to people without HIV.[4–13]

Data from Nigeria and the USA suggest worse clinical outcomes in people with more HIV-related immunosuppression.[4,14–16] Two reports from Nigeria during the 2017–18 outbreak suggested that people with advanced

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*Contributed equally

Skin Neglected Tropical diseases and Sexually Transmitted Infections section, Fight Infectious Diseases Foundation (O Mitjà PhD, A Alemany MD, C Galvan-Casas MD), **and Infectious Disease Department, Fight Infectious Diseases Foundation** (R Paredes PhD), **University Hospital Germans Trias i Pujol, Badalona, Spain; Clinical Research Department, London School of Hygiene & Tropical Medicine, London, UK** (M Marks PhD); **Hospital for Tropical Diseases, and Division of Infection and Immunity, University College London Hospitals, London, UK** (M Marks); **Clínica Especializada Condesa Cuauhtémoc, Mexico City, Mexico** (J I Lezama Mora MD); **Clínica Especializada Condesa Iztapalapa, Mexico City, Mexico** (J C Rodríguez-Aldama MD); **Instituto Nacional de Infectología Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil** (M S Torres Silva MD); **Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, México City, México** (E A Corral Herrera MD, Prof B Crabtree-Ramirez MD); **Infectious Diseases Department, Hospital Clínic de Barcelona, Barcelona University, Barcelona, Spain** (Prof J Lu Blanco PhD); **Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain** (Prof J Lu Blanco); **Institut d'Investigacions Mèdiques August Pi i Sunyer,**

Mpox in people with advanced HIV infection: a global case series

- A network of clinicians from 19 countries provided data of confirmed mpox cases between May 11, 2022, and Jan 18, 2023, in adult PLWH with CD4 <350/mm3 or CDC stage C
- 382 cases: 367 cisgender men, four cisgender women, and ten transgender women.
  - Median age of (IQR 30–43) years, median CD4 211 (IQR 117–291) cells per mm3. 193 (51%) had undetectable viral load.
- **Severe complications were more common in people with CD4<100 cells/mm3 than in those with >300/ mm3: including necrotising skin lesions (54% vs 7%), lung involvement (29% vs 0%) occasionally with nodules, and secondary infections and sepsis (44% vs 9%).**
- Overall, **107 (28%) of 382 were hospitalised, of whom 27 (25%) died**. All deaths occurred in people with CD4 counts of less than 200 cells per mm3. Among people with CD4 counts of less than 200 cells per mm3, more deaths occurred in those with high HIV viral load.
- **An IRIS to mpox was suspected in 21 (out of 85, 25%) → 12 (out of 21, 57%) died.**
- 62 (16%) of 382 received tecovirimat and seven (2%) received cidofovir or brincidofovir. Three individuals had laboratory confirmation of tecovirimat resistance.

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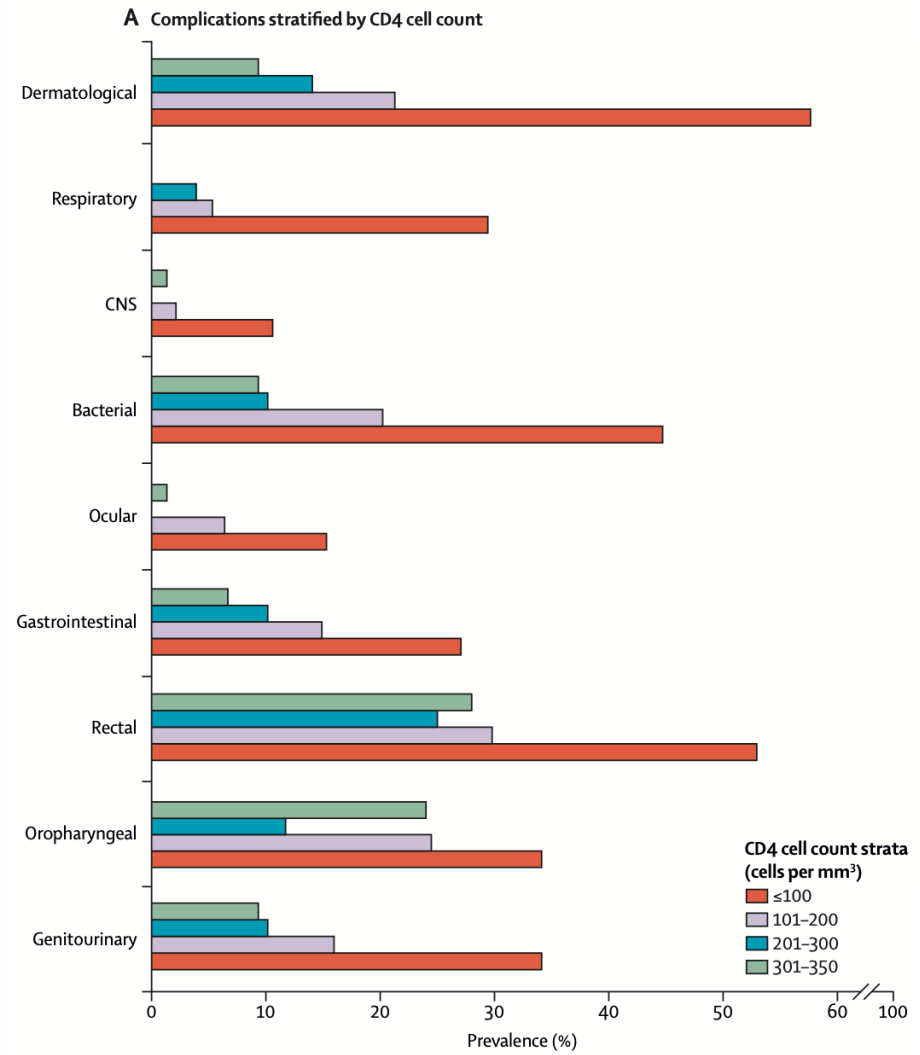
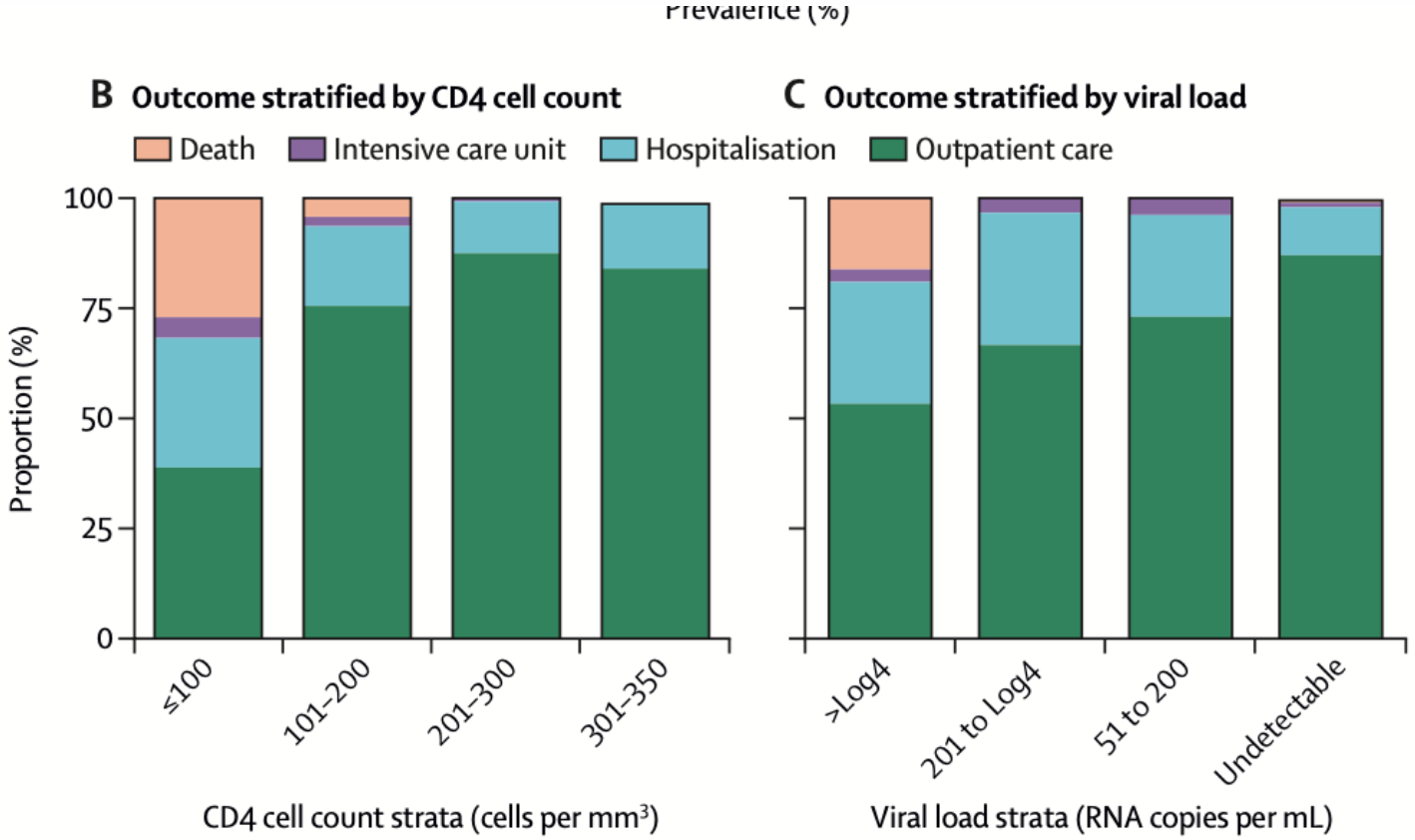
Mpox in people with advanced HIV infection: a global case series





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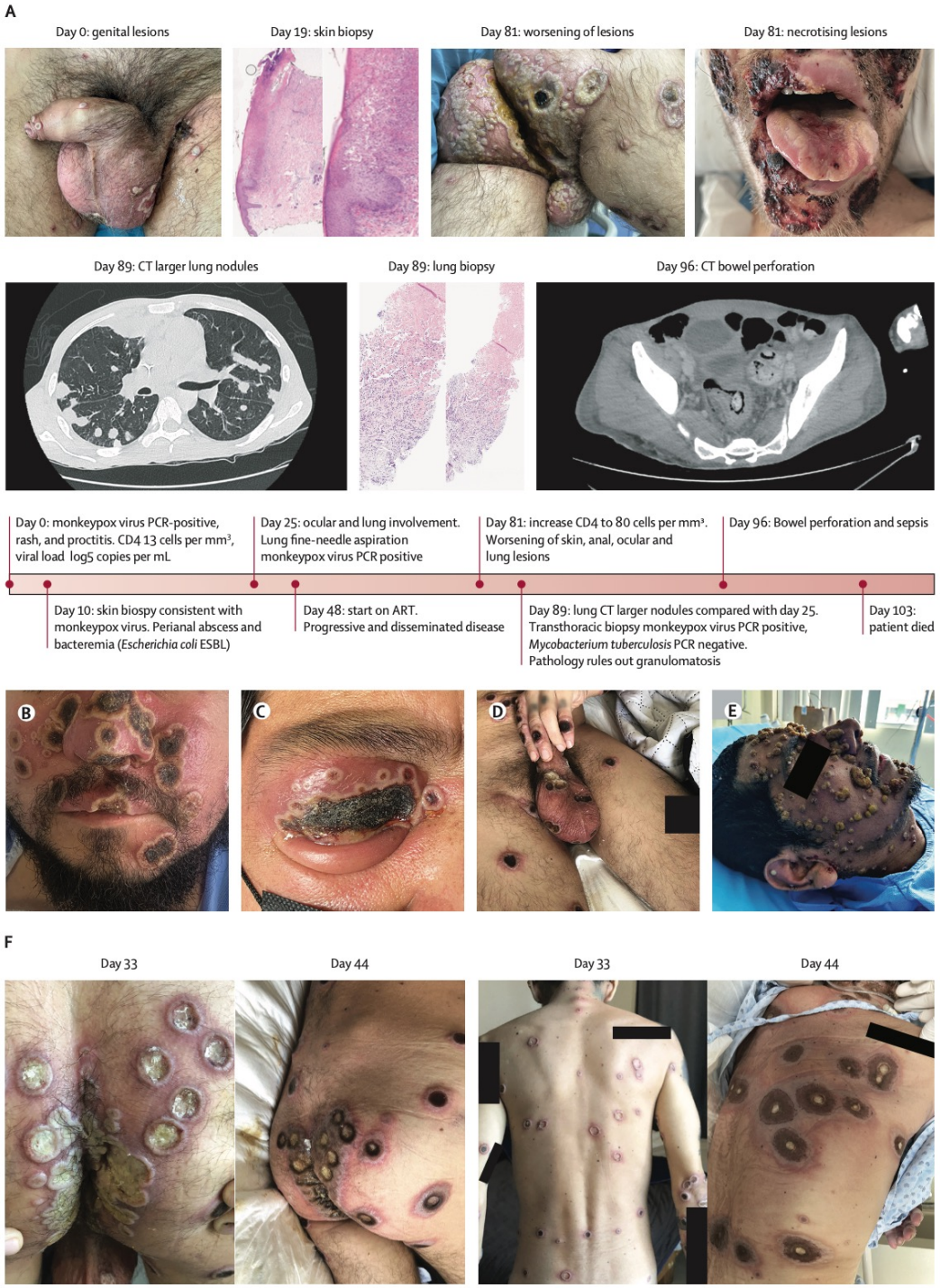

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Mpox in people with advanced HIV infection: a global case series

- A network of clinicians from 19 countries provided data of confirmed mpox cases between May 11, 2022, and Jan 18, 2023, in adult PLWH with CD4 <350/mm3 or CDC stage C
- 382 cases: 367 cisgender men, four cisgender women, and ten transgender women.
  - Median age of (IQR 30–43) years, median CD4 211 (IQR 117–291) cells per mm3. 193 (51%) had undetectable viral load.
- **Severe complications were more common in people with CD4<100 cells/mm3 than in those with >300/ mm3: including necrotising skin lesions (54% vs 7%), lung involvement (29% vs 0%) occasionally with nodules, and secondary infections and sepsis (44% vs 9%).**
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- **An IRIS to mpox was suspected in 21 (out of 85, 25%) → 12 (out of 21, 57%) died.**
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Original Article

ORIGINAL ARTICLE

Biomarker associations with insomnia and secondary sleep outcomes in persons with and without HIV in the POPPY-Sleep substudy: a cohort study

Nicholas Bakewell[1], Caroline A Sabin[1,*], Riya Negi[2], Alejandro Garcia-Leon[2], Alan Winston[3], Memory Sachikonye[4], Nicki Doyle[3], Susan Redline[5,6,7], Patrick W.G. Mallon[2,†] and Ken M. Kunisaki[8,9,†]

[1]Institute for Global Health, University College London, London, UK, [2]Centre for Experimental Pathogen Host Research, School of Medicine, University College Dublin, Ireland, [3]Department of Infectious Disease, Imperial College London, London, UK, [4]UK Community Advisory Board (UK-CAB), London, UK, [5]Brigham and Women's Hospital, Boston, USA, [6]Harvard Medical School, Harvard University, Boston, USA, [7]Beth Israel Deaconess Medical Center, Boston, USA, [8]Minneapolis Veterans Affairs Health Care System, Minneapolis, USA and [9]University of Minnesota, Minneapolis, USA

[†]PWGM and KMK are joint senior authors.

[*]Corresponding author. Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, UCL, Royal Free Campus, Rowland Hill Street, London, NW3 2PFUK, UK. Email: c.sabin@ucl.ac.uk

Abstract

Study Objectives: We investigated associations between inflammatory profiles/clusters and sleep measures in people living with HIV and demographically-/lifestyle-similar HIV-negative controls in the Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY)-Sleep substudy.

Methods: Primary outcome was insomnia (Insomnia Severity Index [ISI]>15). Secondary sleep outcomes included 7-day actigraphy (e.g. mean/standard deviation of sleep duration/efficiency), overnight oximetry (e.g. oxygen desaturation index [ODI]) and patient-reported measures (Patient-Reported Outcomes Measurement Information System (PROMIS) sleep questionnaires). Participants were grouped using Principal Component Analysis of 31 biomarkers across several inflammatory pathways followed by cluster analysis. Between-cluster differences in baseline characteristics and sleep outcomes were assessed using Kruskal–Wallis/logistic regression/Chi-squared/Fisher's exact tests.

Results: Of the 465 participants included (74% people with HIV, median [interquartile range] age 54 [50–60] years), only 18% had insomnia and secondary sleep outcomes suggested generally good sleep (e.g. ODI 3.1/hr [1.5–6.4]). Three clusters with distinct inflammatory profiles were identified: "gut/immune activation" (n = 47), "neurovascular" (n = 209), and "reference" (relatively lower inflammation; n = 209). The "neurovascular" cluster included higher proportions of people with HIV, obesity (BMI>30 kg/m^2), and previous cardiovascular disease, mental health disorder, and arthritis of knee/hip relative to the other two clusters. No clinically relevant between-cluster differences were observed in proportions with insomnia (17%, 18%, 20%) before (p = .76) or after (p = .75) adjustment for potential confounders. Few associations were observed among actigraphy, oximetry, and PROMIS measures.

Conclusions: Although associations could exist with other sleep measures or biomarker types not assessed, our findings do not support a strong association between sleep and inflammation in people with HIV.

Statement of Significance

To the best of our knowledge, this is the first study to explore associations between inflammatory profiles identified in a sample of people living with HIV and demographically/lifestyle similar HIV-negative controls and insomnia as well as secondary objective and patient-reported sleep outcomes. Although we do not report clinically or statistically significant associations between patterns of inflammation and insomnia as well as secondary objective and patient-reported sleep outcomes, these findings provide mechanistic insight that allows us to focus future research studies on different inflammatory pathways or biomarker types (e.g. cerebrospinal fluid), and sleep outcomes (e.g. sleep architecture), when exploring associations between inflammation and sleep.

Submitted: 8 April, 2022; **Revised:** 11 August, 2022

POPPY-Sleep Substudy

- The cohort is comprised of two groups of people with HIV: **an older group** aged at least 50 years (a priori designed to comprise approximately 50% of the cohort) and a **younger group** aged 18–49 years (approximately 25% of the cohort) frequency-matched to the older group on sex, ethnicity, sexual orientation and clinic; and **one group of demographically-/lifestyle-similar HIV-negative controls aged at least 50 years (ap- proximately 25% of the cohort) frequency-matched to the older group of people with HIV on age, sex, sexual orientation ethnicity and geographical location**
- n= 483
  - Participants attended one study visit between March 2017 and July 2018, where they completed questionnaires on sleep quality, symptoms for sleep disorders, sleep medical history and medication use for sleep problems. Assessment of anthropometric measurements and cognitive function was also conducted during the visit. The study visit was followed by **in-home procedures including a daily sleep diary, actigraphy and oximetry measurements, and another visit to return completed sleep diaries and devices**. In addition, fasting plasma samples were collected from participants at or near the time of POPPY- Sleep sub-study enrollment and stored in ultra-low temperature freezers for biomarker assessments.

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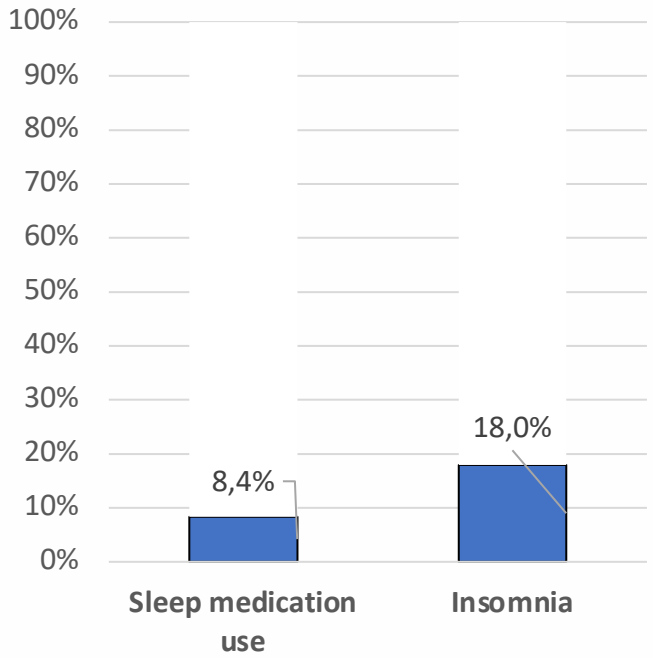
POPPY - Sleep Substudy

- 465 (out of 483) participants had reliable biomarker measurements and were included in the analyses
  - 343 (74%) people with HIV → median (interquartile range [IQR]) age 54 [50–60] years)
  - Most were male (80%), men who have sex with men (MSM) (71%) and white (88%)



Odds ratio (OR (95% CI)) or median [Q1-Q3], unless otherwise noted	Overall (*n* = 465)*
PRIMARY SLEEP OUTCOME: Insomnia (ISI>15)	
Logistic Regression Results, *Estimated OR of Insomnia (95% CI)*	
Unadjusted	--
Adjusted (HIV status, age, sex, race)	--
SECONDARY SLEEP OUTCOMES: PROMIS, Actigraphy and Oximetry	
PROMIS Questionnaire T-scores, *median [Q1-Q3]*	
Sleep-Related Impairment T-score	49.0 [44.0–56.0]
Sleep Disturbance T-score	51.0 [46.0–57.0]
Actigraphy, *median [Q1-Q3]*	
Mean wake after sleep onset (WASO;mins)	53.0 [39.0–73.0]
SD of wake after sleep onset (WASO;mins)	19.0 [13.0–28.0]
Mean length of awakenings (mins)	3.0 [2.5–3.7]
SD of length awakenings (mins)	0.8 [0.6–1.2]
Mean number of awakenings	18.0 [14.0–23.0]
SD of number of awakenings	5 [4.0–7.0]
Mean sleep duration (mins)	423.0 [384.0–458.0]
SD of sleep duration (mins)	54.0 [39.0–80.0]
Mean sleep maintenance efficiency (%)	89.0 [85.1–91.6]
SD of sleep maintenance efficiency (%)	3.5 [2.4–4.9]
Mean sleep onset latency (mins)	7.0 [6.0–9.0]
SD of sleep onset latency(mins)	3.0 [2.0–5.0]
Mean movement index (%)	17.2 [13.7–21.6]
SD of movement index (%)	3.4 [2.4–4.9]
Oximetry, *median [Q1–Q3]*	
Oxygen Desaturation Index (ODI) (4% Desaturation) (events per hour)	3.1 [1.5–6.4]
Percentage of time with SpO2 below 90%	0.3 [0.0–2.5]

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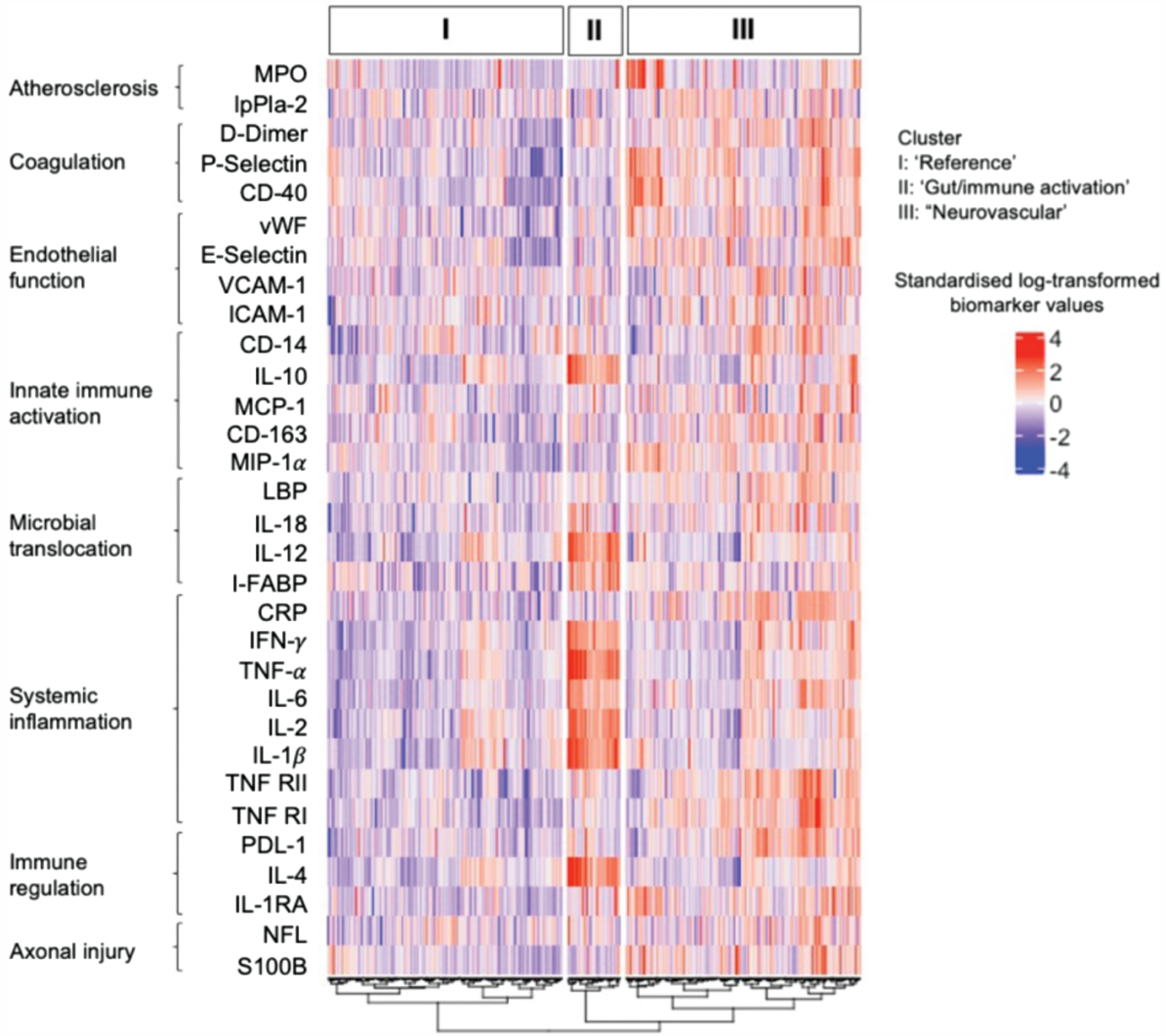
POPPY - Sleep Substudy

Reference cluster
45%

no distinct upregulation in inflammatory pathways



Gut/Immune activation cluster
10%

upregulation of cytokines and biomarkers associated with gut microbial translocation as well as regulation of responses to immune activation and proinflammatory cytokines

Neurovascular cluster
45%

upregulation in markers including coagulation, vascular as well as neuronal markers

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n (%) or median [Q1-Q3], unless otherwise noted	Overall (*n* = 465)*	Cluster			*p*†
		"Gut/immune activation" (*n* = 47)	"Neurovascular" (*n* = 209)	'Reference (*n* = 209)	
Demographics					
Age in years	54 [50–60]	56 [52–61]	55 [50–60]	54 [48–60]	.08
Male	374 (80.4%)	32 (68.1%)	170 (81.3%)	172 (82.3%)	.08
White	408 (87.7%)	41 (87.2%)	178 (85.2%)	189 (90.4%)	.26
Living with HIV	343 (73.8%)	28 (59.6%)	163 (78.0%)	152 (72.7%)	.03
Anthropometric Measurements					
Obese (BMI ≥30 kg/m^2)	82 (17.8%)	10 (21.3%)	50 (24.3%)	22 (10.6%)	.001
Systolic Blood Pressure (mmHg)	126 [117–140]	135 [125–154]	126 [116–138]	126 [116–138]	.002
Diastolic Blood Pressure (mmHg)	79 [72–86]	82 [73–90]	79 [70–86]	78 [72–84]	.23
Lifestyle Factors					
MSM sexuality/route of HIV transmission	332 (71.4%)	30 (63.8%)	147 (70.3%)	155 (74.2%)	.33
Current alcohol use	384 (82.6%)	41 (87.2%)	168 (80.4%)	175 (83.7%)	.45
History of recreational drug use in past 6 months	107 (23.0%)	8 (17.0%)	55 (26.3%)	44 (21.1%)	.26
Ever injected drugs[FE]	32 (6.9%)	2 (4.3%)	16 (7.7%)	14 (6.7%)	.77
Comorbidities					
History of cancer	58 (12.5%)	6 (12.8%)	33 (15.8%)	19 (9.1%)	.12
History of any AIDS event	96 (20.6%)	8 (17.0%)	52 (24.9%)	36 (17.2%)	.13
History of any mental health disorder	175 (37.6%)	14 (29.8%)	96 (45.9%)	65 (31.1%)	.004
History of chest disease	173 (37.2%)	13 (27.7%)	87 (41.6%)	73 (34.9%)	.13
History of any thyroid disease[FE]	18 (3.9%)	1 (2.1%)	9 (4.3%)	8 (3.8%)	.94
History of renal problems[FE]	7 (1.5%)	1 (2.1%)	5 (2.4%)	1 (0.5%)	.21
History of any diabetes[FE]	33 (7.1%)	1 (2.1%)	21 (10.0%)	11 (5.3%)	.07
History of Hepatitis B Virus	69 (14.8%)	8 (17.0%)	29 (13.9%)	32 (15.3%)	.83
History of Hepatitis C Virus[FE]	29 (6.2%)	4 (8.5%)	14 (6.7%)	11 (5.3%)	.64
History of cardiovascular disease	206 (44.3%)	13 (27.7%)	111 (53.1%)	82 (39.2%)	.001
History of arthritis of knee or hip	54 (11.6%)	4 (8.5%)	34 (16.3%)	16 (7.7%)	.02
Sleep Medication					
Sleep medication use for insomnia[FE]	39 (8.4%)	2 (4.3%)	15 (7.2%)	22 (10.5%)	.33

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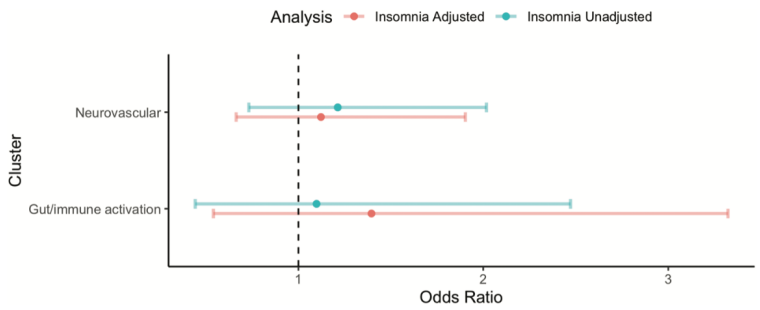
POPPY - Sleep Substudy



Odds ratio (OR (95% CI)) or median [Q1-Q3], unless otherwise noted	Overall (*n* = 465)*	"Gut/immune activation" (*n* = 47)	"Neurovascular" (*n* = 209)	"Reference" (*n* = 209)	*p*†
PRIMARY SLEEP OUTCOME: Insomnia (ISI>15)					
Logistic Regression Results, *Estimated OR of Insomnia (95% CI)***					
Unadjusted	--	1.10 (0.44, 2.47)	1.21 (0.73, 2.02)	**REF**	.76
Adjusted (HIV status, age, sex, race)	--	1.40 (0.54 3.32)	1.12 (0.66, 1.90)	**REF**	.75
SECONDARY SLEEP OUTCOMES: PROMIS, Actigraphy and Oximetry					
PROMIS Questionnaire T-scores, *median [Q1-Q3]*					
Sleep-Related Impairment T-score	49.0 [44.0–56.0]	47.3 [43.6–52.9]	50.3 [43.6–57.2]	48.9 [43.6–54.0]	.17
Sleep Disturbance T-score	51.0 [46.0–57.0]	50.1 [45.5–58.0]	52.2 [45.5–57.3]	49.0 [44.2–56.3]	.25
Actigraphy, *median [Q1-Q3]*					
Mean wake after sleep onset (WASO;mins)	53.0 [39.0–73.0]	54.0 [40.0–67.0]	57.0 [41.3–78.0]	49.0 [38.0–70.3]	.08
SD of wake after sleep onset (WASO;mins)	19.0 [13.0–28.0]	20.0 [13.0–24.0]	21.0 [14.0–30.0]	17.0 [12.0–26.0]	.01
Mean length of awakenings (mins)	3.0 [2.5–3.7]	3.1 [2.6–3.7]	3.3 [2.7–4.1]	2.8 [2.3–3.5]	<.001
SD of length awakenings (mins)	0.8 [0.6–1.2]	0.8 [05–1.3]	0.9 [0.7–1.4]	0.7 [0.5–1.0]	<.001
Mean number of awakenings	18.0 [14.0–23.0]	18.0 [14.0–22.0]	18 [13.0–22.0]	18.0 [14.0–24.0]	.42
SD of number of awakenings	5 [4.0–7.0]	5.0 [4.0–6.0]	5.0 [4.0–7.0]	5.0 [4.0–7.0]	.65
Mean sleep duration (mins)	423.0 [384.0–458.0]	428.0 [406.0–455.3]	423.5 [377.3–462.3]	421.0 [386.5–455.3]	.60
SD of sleep duration (mins)	54.0 [39.0–80.0]	46.0 [39.0–73.0]	60.0 [39.0–85.8]	52.0 [38.8–75.0]	.16
Mean sleep maintenance efficiency (%)	89.0 [85.1–91.6]	89.2 [86.9–91.9]	88.4 [83.6–91.4]	89.8 [85.6–91.8]	.10
SD of sleep maintenance efficiency (%)	3.5 [2.4–4.9]	3.3[2.3–4.5]	3.8 [2.5–5.3]	3.3[2.3–4.7]	.10
Mean sleep onset latency (mins)	7.0 [6.0–9.0]	7.0 [6.0–8.0]	7.0 [6.0–9.0]	7.0 [6.0–9.0]	.63
SD of sleep onset latency(mins)	3.0 [2.0–5.0]	4.0 [2.0–5.0]	3.0 [2.0–6.0]	3.0 [2.0–5.0]	.53
Mean movement index (%)	17.2 [13.7–21.6]	16.7 [14.2–19.9]	17.8 [13.7–22.8]	16.5 [13.6–20.4]	.15
SD of movement index (%)	3.4 [2.4–4.9]	3.4 [2.3–4.3]	3.7 [2.6–5.7]	3.3 [2.3–4.6]	.008
Oximetry, *median [Q1–Q3]*					
Oxygen Desaturation Index (ODI) (4% Desaturation) (events per hour)	3.1 [1.5–6.4]	2.4 [1.4–7.5]	3.6 [1.5–6.7]	3.0 [1.5–6.0]	.50
Percentage of time with SpO2 below 90%	0.3 [0.0–2.5]	0.1 [0.0–1.6]	0.5 [0.0–4.7]	0.2 [0.0–1.7]	.009

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The Journal of Infectious Diseases
MAJOR ARTICLE

The IDOze Study: The Link Between Sleep Disruption and Tryptophan-Kynurenine Pathway Activation in Women With Human Immunodeficiency Virus

Andrea C. Rogando,[1,2] Kathleen M. Weber,[2] Jiaqian Xing,[3] Xiaonan Xue,[3] Tsion Yohannes,[2] Ralph Morack,[2] Qibin Qi,[3] Clary Clish,[4,©] Kevin Bullock,[4] Deborah Gustafson,[5] Kathryn Anastos,[6] Anjali Sharma,[6] Helen J. Burgess,[7] and Audrey L. French[8]

[1]College of Science and Health at Charles R. Drew University of Medicine and Science, Los Angeles, California, USA; [2]Hektoen Institute of Medicine/CORE Center of Cook County Health, Chicago, Illinois, USA; [3]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA; [4]Metabolomics Platform, Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, USA; [5]Department of Neurology, State University of New York Downstate Medical Center, Brooklyn, New York, USA; [6]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA; [7]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA; and [8]Department of Medicine, Stroger Hospital of Cook County Health, Chicago, Illinois, USA

Background. Poor sleep is associated with human immunodeficiency virus (HIV), particularly among women with HIV (WWH), although mechanisms are unclear. We explored cross-sectional associations between sleep disruption and tryptophan-kynurenine (T/K) pathway activation, measured by the kynurenine-to-tryptophan ratio (K:T).

Methods. HIV-uninfected women (HIV^-) and WWH aged 35–70 years and on stable antiretroviral therapy were included. Sleep metrics were measured using wrist actigraphy. Plasma T/K pathway metabolites were measured using liquid chromatography–tandem mass spectrometry. Multivariate linear regression models examined relationships between K:T and actigraphy-based sleep metrics by HIV status.

Results. WWH (n = 153) and HIV^- women (n = 151) were demographically similar. Among WWH, median CD4 was 751 cells/μL; 92% had undetectable HIV RNA. Compared to HIV^- women, WWH had higher K:T ($P < .001$) and kynurenine ($P = .01$) levels but similar tryptophan levels ($P = .25$). Higher K:T was associated with more wake bouts ($P = .001$), more time awake after sleep onset ($P = .01$), and lower sleep efficiency ($P = .03$) in WWH only.

Conclusions. HIV infection was associated with T/K pathway activation; this activation was associated with poorer sleep efficiency and more fragmented sleep. While longitudinal studies are needed to elucidate the directionality of these associations, these findings may help identify treatments to reduce sleep disruption in WWH by targeting residual inflammation and T/K pathway activation.

Keywords. HIV infection; women; sleep; metabolomics; kynurenine; tryptophan; IDO-1; indoleamine 2, 3-dioxygenase.

Despite significant improvements in longevity and quality of life associated with suppressive antiretroviral therapy (ART), persons with human immunodeficiency virus (PWH) still suffer from a higher burden of sleep and circadian disruption than persons without human immunodeficiency virus (HIV). In a study of 1682 women with HIV (WWH) and well-matched HIV-uninfected (HIV^-) women, WWH were 17% more likely to report insomnia symptoms than HIV^- women [1]. WWH and PWH aged >40 years are particularly affected by sleep disturbances [2]. Sleep disturbances characterized by shorter sleep duration and poor sleep continuity as well as significant circadian dysregulation, as evidenced by abnormally high night-to-night variability in sleep timing, have been observed in PWH [3]. These data suggest that there may be a mechanism common to PWH that plays a role in sleep and circadian disruption [4].

The tryptophan-kynurenine (T/K) pathway is a major route by which tryptophan (TRP) is catabolized. It is driven in multiple cell types by indoleamine 2,3-dioxygenase (IDO) [5]. Prior work by our group and others found that the T/K pathway is disrupted in HIV [6–8]. These studies have reported an elevated kynurenine-to-tryptophan ratio (K:T) in PWH, likely reflecting increased IDO activity [7, 8]. These observations are supported by findings that HIV Tat protein and inflammatory molecules such as interferon gamma (IFN-γ), tumor necrosis factor alpha receptor II (TNF-RII), and interleukin 6 (IL-6) induce IDO expression [9, 10]. T/K pathway activation by IDO [9, 10] triggers TRP catabolism, causing accumulation of kynurenine (KYN) and downstream metabolites, including potentially neurotoxic quinolinic acid (QUIN) [11]; in HIV^- persons, sleep disruption has been found to be associated

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Correspondence: Audrey French, MD, Stroger Hospital of Cook County, 1950 W Polk St, Rm 6902, Chicago, IL 60612, USA (afrench@cookcountyhhs.org).
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BRAIN
ORIGINAL ARTICLE

Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

Robert K. Heaton,[1] Ronald J. Ellis,[1,2] Bin Tang,[1] Christina M. Marra,[3] Leah H. Rubin,[4] David B. Clifford,[5] J. Allen McCutchan,[6] Benjamin B. Gelman,[7,8] Susan Morgello,[9] Donald R. Franklin,[1] and Scott L. Letendre[1,6]

See Cysique and Brew (https://doi.org/10.1093/brain/awad035) for a scientific commentary on this article.

Modern antiretroviral therapy (ART) has increased longevity of people with HIV and shifted the age distribution of the HIV pandemic upward toward that of the general population. This positive development has also led to concerns about premature and/or accelerated neurocognitive and physical ageing due to the combined effects of chronic HIV, accumulating comorbidities, adverse effects or possible toxicities of ART and biological ageing. Here we present results of comprehensive assessments over 12 years of 402 people with HIV in the CNS HIV ART Effects Research (CHARTER) programme, who at follow-up were composed of younger (<60 years) and older (≥60 years) subgroups.

Over the 12 years, ART use and viral suppression increased in both subgroups as did systemic and psychiatric comorbidities; participants in both subgroups also evidenced neurocognitive decline beyond what is expected in typical ageing. Contrary to expectations, all these adverse effects were comparable in the younger and older CHARTER subgroups, and unrelated to chronological age. Neurocognitive decline was unrelated to HIV disease or treatment characteristics but was significantly predicted by the presence of comorbid conditions, specifically diabetes, hypertension, chronic pulmonary disease, frailty, neuropathic pain, depression and lifetime history of cannabis use disorder. These results are not consistent with premature or accelerated neurocognitive ageing due to HIV itself but suggest important indirect effects of multiple, potentially treatable comorbidities that are more common among people with HIV than in the general population.

Good medical management of HIV disease did not prevent these adverse outcomes, and increased attention to a range of comorbid conditions in people with HIV may be warranted in their care.

1 Department of Psychiatry, University of California San Diego, San Diego, CA 92093, USA
2 Department of Neurosciences, University of California, San Diego, CA 92093, USA
3 Department of Neurology, University of Washington, Seattle, WA 98104, USA
4 Department of Neurology, Johns Hopkins University, Baltimore, MD 21218, USA
5 Department of Neurology, Washington University at St. Louis, St. Louis, MO 63110, USA
6 Department of Medicine, University of California San Diego, San Diego, CA 92093, USA
7 Department of Pathology, University of Texas Medical Branch, Galveston, TX 77555, USA
8 Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX 77555, USA
9 Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Correspondence to: Scott Letendre, MD
University of California, San Diego
220 Dickinson Street, Suite A
San Diego, California 92103, USA
E-mail: sletendre@ucsd.edu

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Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

	Younger (<60 years)		Older (≥60 years)		Age group	Visit	Age group × Visit	Group contrasts[a]
	(*n* = 260)		(*n* = 142)		*P*-value	*P*-value	*P*-value	
Characteristic	Baseline (1)	12 years (2)	Baseline (3)	12 years (4)				
Age, years	39.2 (5.30)	51.8 (5.47)	51.5 (4.59)	64.4 (4.34)	<0.001	<0.001	0.018	1 < 2,3; 4 > 2,3
Education, years	12.8 (2.53)	Unchanged	13.5 (2.73)	Unchanged	0.005	No test	No test	1 < 3
Sex, male	197 (75.8%)	Unchanged	110 (77.5%)	Unchanged	0.81	No test	No test	No diff.
Race, Black	118 (45.4%)	Unchanged	67 (47.2%)	Unchanged	0.75	No test	No test	No diff.
Ethnicity, Hispanic	32 (12.3%)	Unchanged	11 (7.8%)	Unchanged	0.18	No test	No test	No diff.
WRAT-III	92.3 (15.3)	92.5 (15.4)	91.6 (17.7)	92.1 (18.2)	0.68	0.63	0.57	No diff.
Global Deficit Score[b]	0.50 (0.50)	0.53 (0.57)	0.51 (0.46)	0.55 (0.54)	0.59	0.88	0.82	No diff.
Global impairment	116 (44.6%)	104 (40.5%)	65 (45.8%)	65 (46.4%)	0.81	0.25	0.39	No diff.
BDI-II	13.5 (10.8)	9.55 (9.35)	13.2 (11.0)	9.83 (10.0)	0.77	<0.001	0.66	1 > 2; 3 > 4
BDI-II >13	109 (41.9%)	71 (28.1%)	60 (42.3%)	40 (29.0%)	0.95	<0.001	0.99	1 > 2; 3 > 4

Values are mean (SD) or *n* (%). BDI = Beck Depression Inventory; No diff. = no difference; WRAT = Wide Range Achievement Test-III.

[a]Four pairwise comparisons (1 versus 2, 3 versus 4, 1 versus 3, and 2 versus 4) were performed and adjusted using the Benjamini Hochberg procedure.

[b]Square root transformation.

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Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

- At follow-up
- Both groups had lower nadir CD4+ T-cell counts, more AIDS diagnoses, more HCV co-infection, and **more diabetes, hypertension, hyperlipidaemia, CPD, Distal Sensory polyneuropathy, and lifetime cannabis use disorder and major depressive disorder**.
- Clinically favourable changes at follow-up included that many more participants were taking ART with **more frequent HIV suppression and higher CD4+ T-cell counts** and had modestly improved clinical lab indicators (hepatic aspartate transaminase, total protein, and creatinine; haematocrit in the younger group), and **less currently depressed mood** (BDI-II).

The only Age group × Time interactions of possible consequence were unfavourable for the younger group: **nadir CD4+ T-cell count declined more, and lifetime alcohol use disorder increased more than in the older group at follow-up.**

Importantly, and contrary to expectations, cross-sectional GDS and rate of neurocognitive impairment were high for both groups at both time points but did not evidence significant differences between the age groups or the time points and did not show an Age group × Time interaction

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Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

	Younger (<60 years) (n = 260)		Older (≥60 years) (n = 142)		Age group	Visit	Age group × Visit	Group contrasts[a]
Characteristic	Baseline (1)	12 years (2)	Baseline (3)	12 years (4)	P-value	P-value	P-value	
HCV seropositive	50 (19.2%)	84 (32.4%)	45 (31.7%)	62 (44.0%)	0.013	<0.001	0.43	1 < 2,3; 4 > 2,3
Diabetes	18 (6.9%)	46 (17.8%)	8 (5.6%)	36 (25.5%)	0.82	<0.001	0.073	1 < 2; 3 < 4
Hypertension	42 (16.2%)	121 (46.7%)	33 (23.2%)	87 (61.7%)	0.091	<0.001	0.46	1 < 2; 3 < 4; 2 < 4
Hyperlipidaemia	19 (7.3%)	89 (34.4%)	20 (14.1%)	70 (49.6%)	0.039	<0.001	0.94	1 < 2,3; 4 > 2,3
CPD	23 (8.8%)	49 (18.9%)	14 (9.9%)	33 (23.4%)	0.60	<0.001	0.55	1 < 2; 3 < 4
Neuropathic pain	67 (25.8%)	82 (31.9%)	52 (36.9%)	64 (45.7%)	0.019	0.059	0.81	1 < 3; 2 < 4
Distal sensory neuropathy	50 (27.2%)	91 (50.3%)	53 (60.2%)	86 (78.2%)	<0.001	<0.001	0.75	1 < 2,3; 4 > 2,3
Charlson Comorbidity Index	7.47 (3.37)	9.65 (3.31)	8.57 (3.35)	11.3 (3.14)	0.002	<0.001	0.047	1 < 2,3; 4 > 2,3
VACS Index[b]	18.1 (15.0)	24.4 (16.4)	25.1 (14.7)	36.8 (18.3)	<0.001	<0.001	0.12	1 < 2,3; 4 > 2,3
Framingham CVD Risk	No data	14.4 (12.0)	No data	23.0 (14.8)	<0.001	No test	No test	2 < 4
Framingham Stroke Risk	No data	5.48 (5.00)	No data	11.7 (11.0)	<0.001	No test	No test	2 < 4
Metabolic syndrome	191 (73.5%)	181 (69.9%)	112 (78.9%)	100 (71.4%)	0.22	0.28	0.46	No diff.
Prefrail	No data	118 (45.7%)	No data	68 (48.2%)	0.32	No test	No test	No diff.
Frail	No data	14 (5.4%)	No data	15 (10.6%)	0.069	No test	No test	No diff.
Lifetime MDD	128 (49.4%)	168 (65.4%)	64 (45.4%)	80 (57.1%)	0.39	<0.001	0.39	1 < 2; 3 < 4
Current MDD	37 (14.3%)	16 (6.69%)	14 (9.93%)	12 (9.38%)	0.21	0.003	0.082	1 > 2
Lifetime alcohol disorder	132 (51.0%)	149 (58.0%)	79 (56.0%)	81 (57.9%)	0.92	<0.001	<0.001	1 < 2
Current alcohol disorder	4 (1.54%)	3 (1.26%)	1 (0.71%)	1 (0.78%)	0.48	0.78	0.85	No diff.
Lifetime cannabis disorder	77 (29.7%)	89 (34.6%)	32 (22.7%)	38 (27.1%)	0.69	<0.001	0.79	1 < 2; 3 < 4
Current cannabis disorder	7 (2.70%)	1 (0.42%)	1 (0.71%)	1 (0.78%)	0.27	0.10	0.21	No diff.
Lifetime meth disorder	42 (16.2%)	50 (19.5%)	12 (8.5%)	12 (8.6%)	0.42	0.014	0.16	1 > 3; 2 > 1,4
Current meth disorder	1 (0.38%)	0 (0.00%)	1 (0.71%)	0 (0.00%)	0.67	1.00	1.00	No diff.
Lifetime any substance use disorder	186 (71.8%)	201 (78.2%)	99 (70.2%)	102 (72.9%)	0.85	<0.001	0.25	1 < 2
Current any substance use disorder	22 (8.5%)	5 (2.1%)	4 (2.8%)	3 (2.3%)	0.039	0.003	0.14	1 > 2
Positive urine drug screen	49 (19.1%)	53 (20.8%)	27 (19.0%)	16 (11.6%)	0.99	0.57	0.059	No diff.

Values are mean (standard deviation) or *n* (%). CVD = cardiovascular disease; MDD = major depressive disorder; meth = methamphetamine; No diff. = no difference.
[a]Four pairwise comparisons (1 versus 2, 3 versus 4, 1 versus 3, and 2 versus 4) were performed and adjusted using the Benjamini Hochberg procedure.
[b]Square root transformation.

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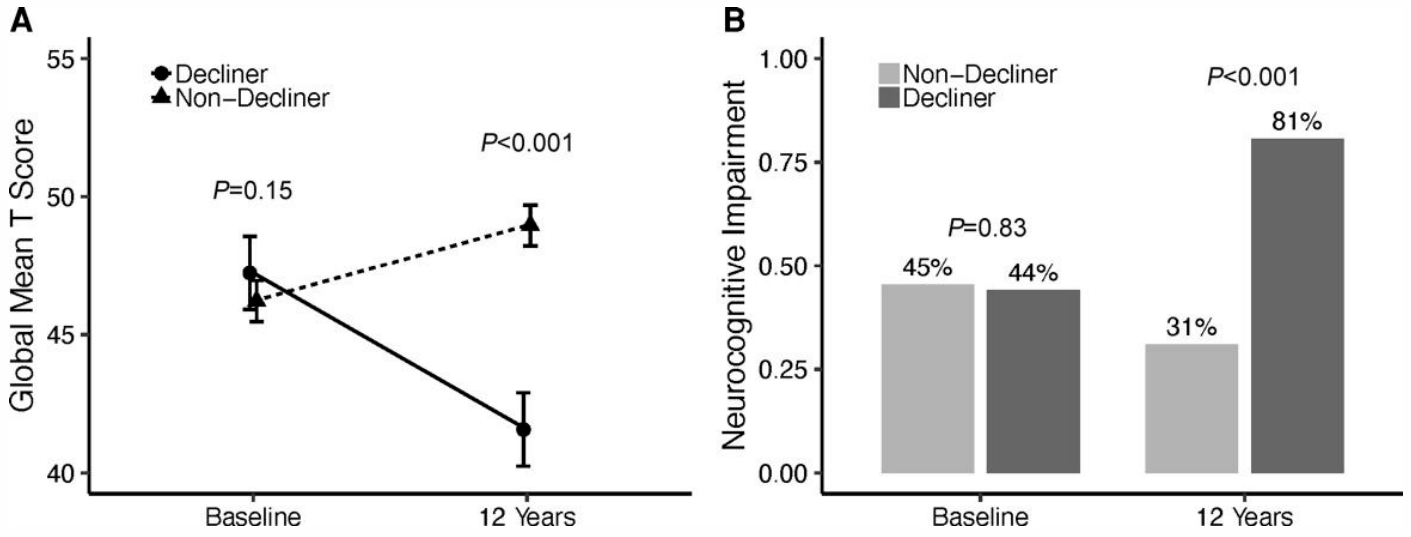
Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

- on average, neurocognitive performance declined modestly over 12 years, regardless of age or age group
- Using GCS and normative data (with 90% CIs) **23.7% declined, 70.0% remained stable, and 6.2% improved**



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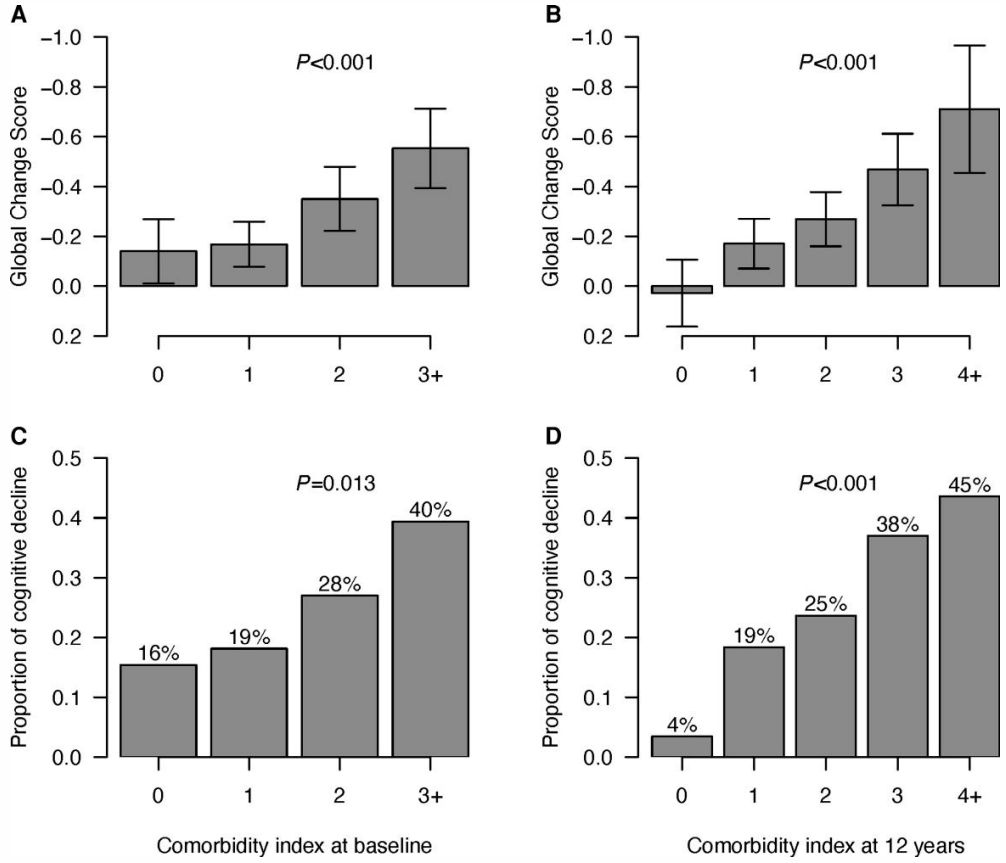
Twelve-year neurocognitive decline in HIV is associated with comorbidities, not age: a CHARTER study

Multivariable linear regression modelling revealed that the following baseline variables most strongly and independently predicted worse GCS over the 12-year follow-up, with a model R2 of 0.050 (P = 0.0034): **hypertension, CPD, BDI-II > 13, lifetime cannabis use disorder, higher serum hepatic aspartate transaminase, and lower serum protein.**



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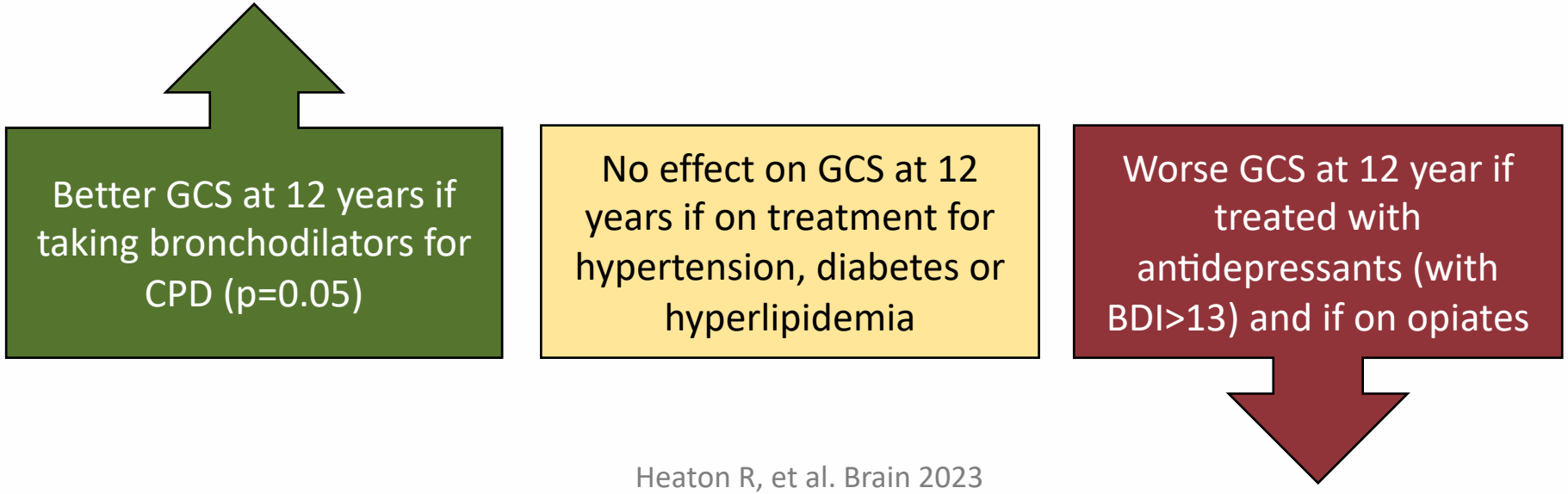
- At 12 years:
  - 111 participants had a BDI-II > 13 → 56 were taking an antidepressant (50.4%)
  - 82 diabetic → 46 were taking an antidiabetic drug (56.1%)
  - 208 hypertension → 158 were taking an antihypertensive drug (75.9%)
  - 82 CPD → 39 were taking a bronchodilator (47.6%)



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Dementias among older males and females in the U.S. Medicare system with and without HIV

Running title: Dementia in Medicare enrollees with HIV

Xiaoying Yu, MD, PhD[1,2], Yong-Fang Kuo, PhD[1,2], Mukaila A. Raji, MD[3], Abbey B. Berenson, MD, PhD [2,4], Jacques Baillargeon, PhD[5], and Thomas P. Giordano, MD, MPH[6,7]

1 Department of Biostatistics & Data Science, University of Texas Medical Branch at Galveston (UTMB), Galveston, TX, USA

2 Center for Interdisciplinary Research in Women's Health, UTMB

3 Department of Internal Medicine, UTMB

4 Department of Obstetrics & Gynecology, UTMB

5 Department of Epidemiology, UTMB

6 Department of Medicine, Baylor College of Medicine, Houston, TX, USA

7 Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX, USA

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Dementias among older males and females in the U.S. Medicare system with and without HIV

- All PLWH >65 years (87216) and 5% PWoH (2.2 M) in Medicare (2007-2019)
- AD/ADRD cases were identified by ICD-9-CM/ICD-10-CM codes
- Both male and female PWH had a significantly higher overall prevalence of AD/ADRD across all years (males with HIV: 26.4%, 95% CI 26.0- 26.7%; females with HIV: 39.4%, 95% CI 38.9-40.0%) compared to PWOH (males: 22.9%, 95% CI 22.8-23.0%; females: 29.4%, 95% CI 29.3-29.8%), with larger differences among females
  - The gap between PWH and PWOH showed an increasing trend over time, was more prominent in females, and increased with age

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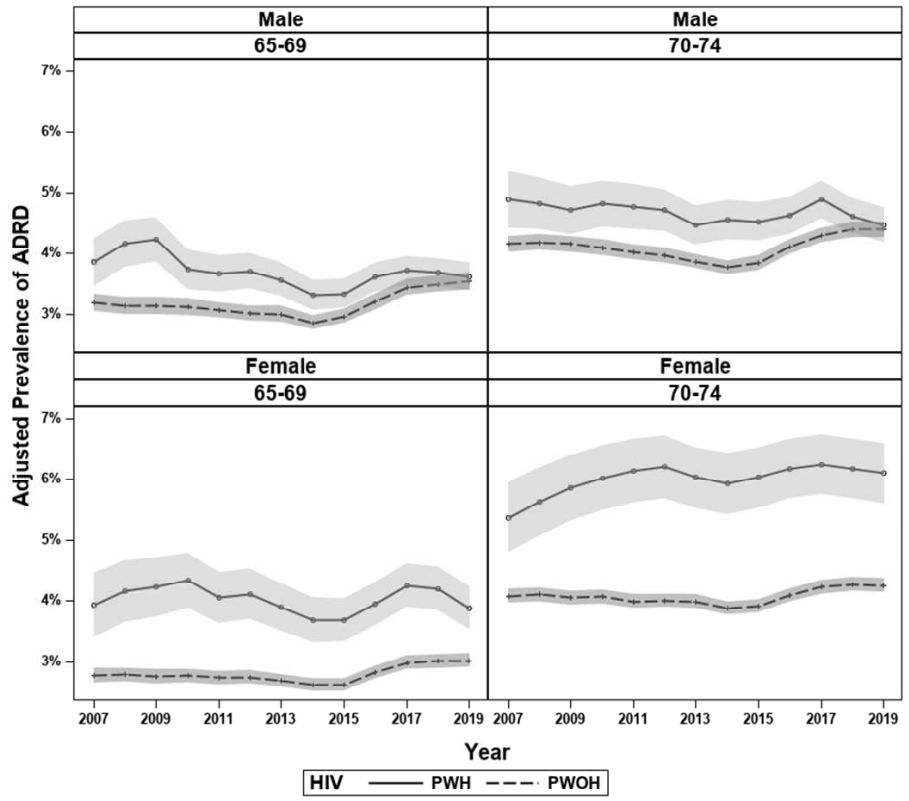
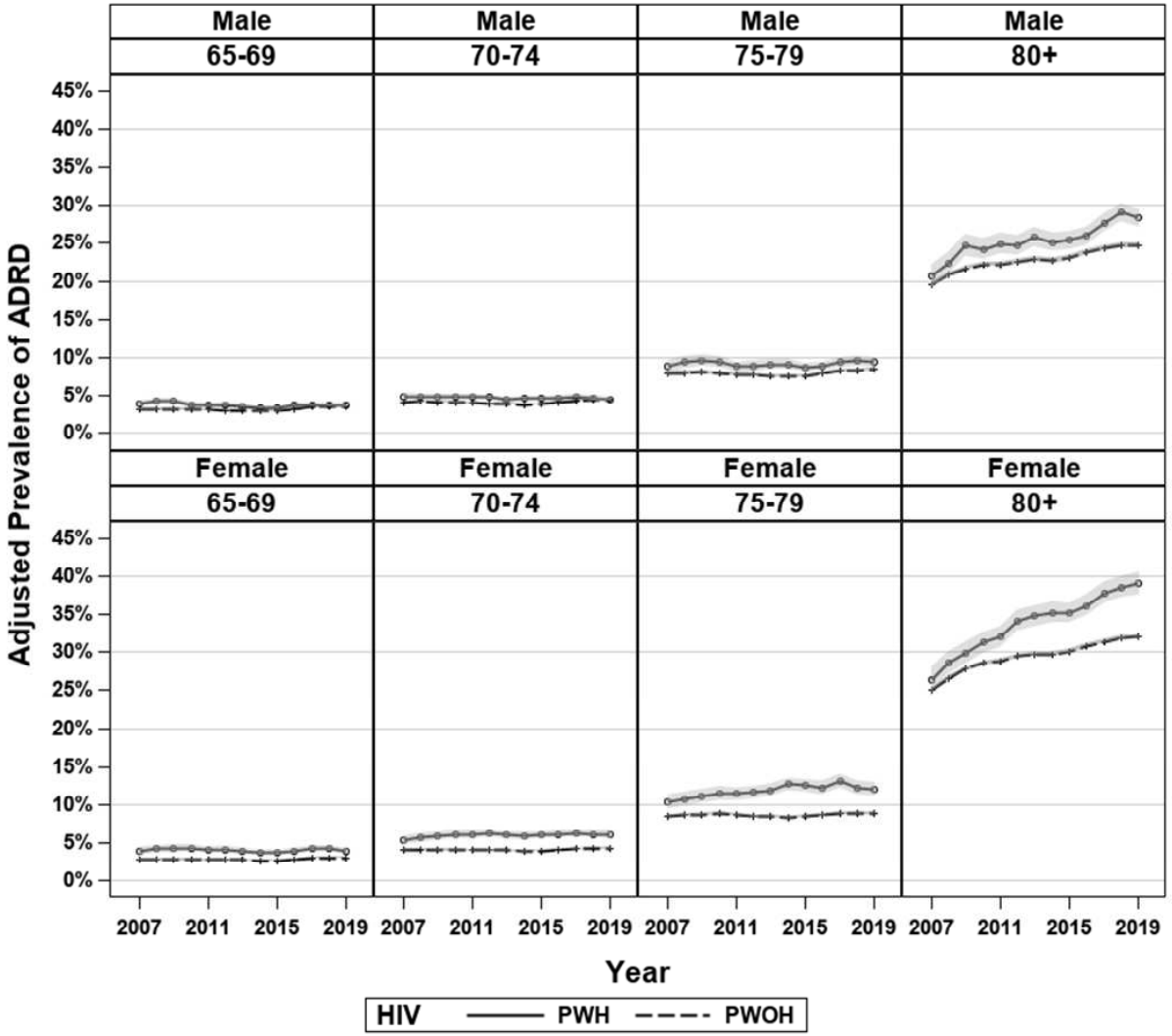
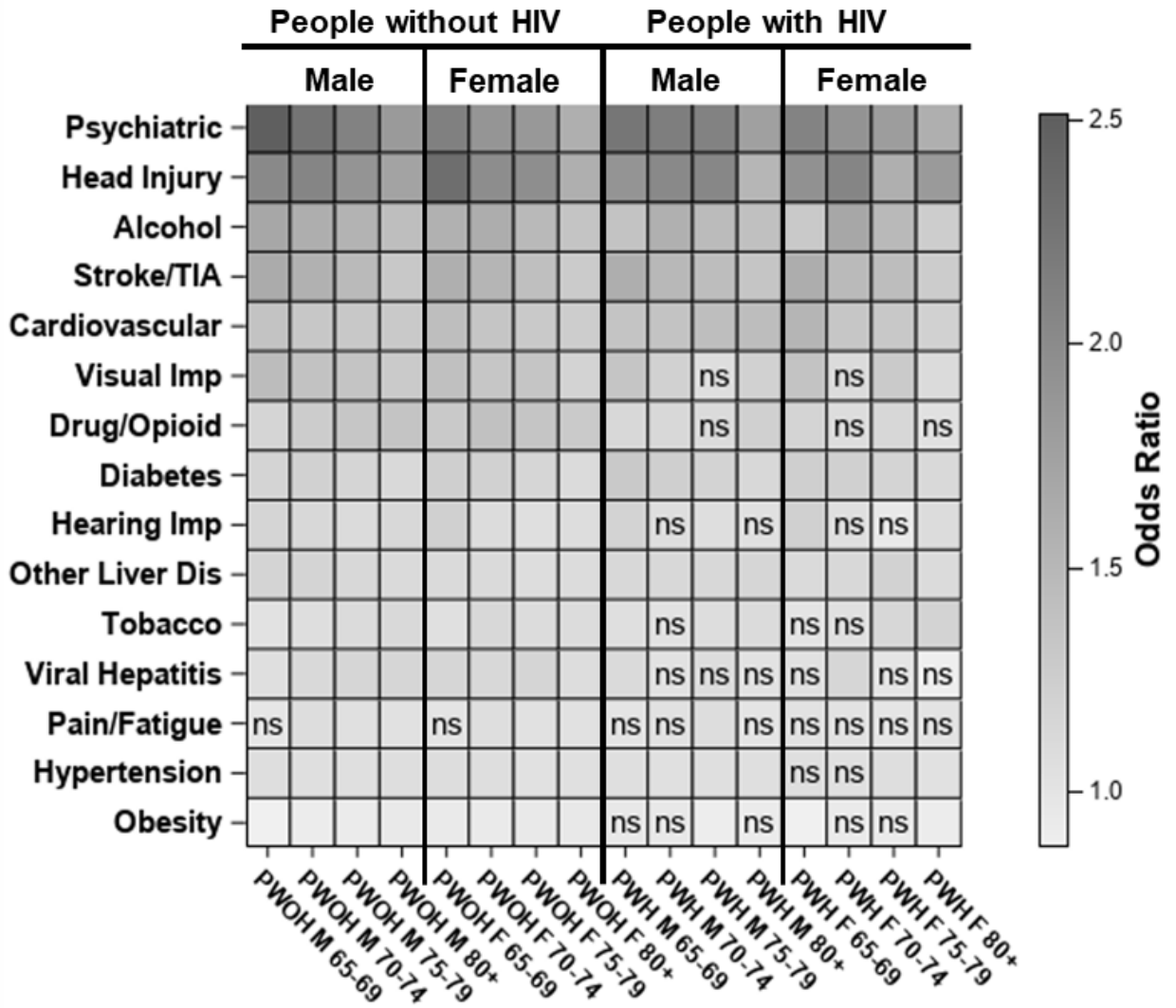
Dementias among older males and females in the U.S. Medicare system with and without HIV





Yu X, et al. JAIDS 2023

Dementias among older males and females in the U.S. Medicare system with and without HIV



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

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

See related paper on page 1457

Background: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) increases low-density lipoprotein cholesterol (LDL-C) and body weight. Metabolic effects of the opposite TAF-to-TDF switch are unknown.

Objectives: To investigate the effect of TAF-to-TDF switch on plasma lipids, body weight, and atherosclerotic cardiovascular disease (ASCVD) risk score.

Design: A retrospective chart review.

Methods: One hundred and forty-six patients with TAF-to-TDF switch (Switch group) were compared with 146 patients matched for sex, age, and third antiretroviral agent class who continued unchanged TAF-containing regimen (Control group). Data were collected at approximately 1 year (follow-up FU-1) and 2 years (follow-up FU-2) after baseline values.

Results: In Switch group at FU-1, total cholesterol (TC) and LDL-C decreased 12.1% and 12.4% ($P < 0.001$ in both), respectively. High-density lipoprotein cholesterol (HDL-C) also decreased 8.2% ($P < 0.001$) in Switch group, but TC/HDL-C ratio did not change. No statistically significant changes were observed in Control group in any lipid values. TC remained similarly decreased through FU-2 in Switch group, but LDL-C increased from FU-1 to FU-2 in both groups. ASCVD risk score decreased from 6.3% at baseline to 6.0% at FU-2 ($P = 0.012$) in Switch group but increased from 8.4 to 9.1% ($P = 0.162$) in Control group. Body weight increased from 83.4 kg at baseline to 84.9 kg at FU-2 ($P = 0.025$) in Control group but remained stable in Switch group (83.1–83.7 kg, $P = 0.978$).

Conclusions: TAF-to-TDF switch improved plasma lipid profile and ASCVD risk score, as well as prevented weight gain, when compared with ongoing TAF-based antiretroviral therapy.

AIDS 2022, **36**:1337–1344

Keywords: body weight, cardiovascular risk score, cholesterol, HIV, tenofovir alafenamide, tenofovir disoproxil fumarate

Introduction

Tenofovir disoproxil fumarate (TDF) has widely been used for treatment of human immunodeficiency virus (HIV) infection for almost two decades, and it remains among the preferred agents in treatment guidelines, together with a newer tenofovir prodrug, tenofovir alafenamide (TAF) [1,2].

Due to pharmacological differences, TAF can be dosed as 1/10th of the TDF dose to reach equivalent intracellular tenofovir concentration [3]. This translates into lower kidney and bone related toxicity when using TAF as compared to TDF [4]. Therefore, TAF has replaced TDF to a large extent in industrialized countries.

Both controlled trials and real-world data have, however, demonstrated worsening of the blood lipid profile after switching from TDF to TAF [5–7]. TDF has been shown to directly decrease blood lipid concentrations [8], whereas the effect of TAF on blood lipids is considered

[a]Department of Infectious Diseases, Inflammation Center, Helsinki University Hospital, and [b]University of Helsinki, Helsinki, Finland.

Correspondence to Kai Juhani Kauppinen, Haartmaninkatu 4, PO Box 372, 00029 Helsinki University Hospital, Helsinki, Finland.
E-mail: kai.kauppinen@fimnet.fi
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EDITORIAL COMMENT

Switch back from TAF to TDF or rather switch forward from metabolic toxicities of drugs to metabolic health of people living with HIV

Jack T. Stapleton[a,b], Roger J. Bedimo[c,d] and Giovanni Guaraldi[e]

See related paper on page 1337

AIDS 2022, **36**:1457–1459

In the past 30 years, lipid abnormalities paralleled the clinical manifestation of HIV disease from wasting syndrome in the pre-ART era, to lipodystrophy in the early ART era, and more recently to weight gain in the contemporary ART scenario. This historical perspective can be also recognized at an individual level: acute and untreated HIV infections are associated with reduced total cholesterol (TC) and high-density lipoprotein-cholesterol (HDL-C) levels and increased triglyceride levels [1–3]. Although effective treatment of HIV may reduce or increase lipid levels depending on the antiretroviral (ARV) regimen employed [4], it must nevertheless be recognized that the impact of HIV and ART on lipids are also related to genetic, environmental and lifestyle factors. Dyslipidemia per se cannot be considered a disease condition but rather, jointly with glucose abnormalities and insulin resistance, should be included under the broad umbrella definition of 'metabolic abnormalities'.

These complex and interrelated biochemical pathways produce tissue damage depicted by ectopic fat accumulation (visceral adipose tissue and liver fat), lean mass reduction (sarcopenia), osteopenia and endothelial dysfunction leading to specific 'metabolic diseases' including obesity, nonalcoholic steatohepatitis, diabetes, osteoporosis, cardiovascular disease, chronic kidney disease, neurocognitive impairment, and frailty. In addition to HIV infection, metabolic abnormalities are also a major driver of systemic inflammation, the so-called meta-inflammation, potentially affecting the natural history of HIV disease.

Different ARV regimens have different metabolic consequences, and due to expected better bone and renal tolerability, tenofovir alafenamide (TAF) has largely replaced tenofovir disoproxil fumarate (TDF) as preferred nucleotide reverse transcriptase inhibitor in initial treatment of ART [5]. Although increases in TC and low-density lipoprotein (LDL) are observed with TAF compared to TDF, the relatively recent findings that TAF was also associated with significant weight gain has been concerning [6].

Do increases in lipid levels and weight gain (and possible metabolic consequences) outweigh the better renal and bone tolerability of TAF compared to TDF? Are these reversible with a switch back to TDF? The current manuscript by Kauppinen *et al.* [7] is an important attempt at answering the second question.

Kauppinen *et al.* [7], in a retrospective, case–control study of 292 subjects, attempted to describe the 'metabolic' impact of the switch back from TAF to TDF assessing the implication of lipids changes on cardiovascular risk assessed with atherosclerotic cardiovascular disease

[a]Departments of Internal Medicine, Microbiology and Immunology, the Iowa City Department of Veterans Affairs Healthcare System, [b]The University of Iowa, Iowa City, IA, [c]Department of Internal Medicine. Veterans Affairs North Texas Healthcare System, [d]University of Texas Southwestern Medical Center in Dallas, Dallas, TX, USA, and [e]Modena HIV Metabolic Clinic (MHMC), Department of Surgical, Medical, Dental and Morphological Sciences University of Modena and Reggio Emilia, Modena, Italy.

Correspondence to Jack T. Stapleton, MD, Department of Internal Medicine, UIHC, SW54-14 GH, 200 Hawkins Drive, Iowa City, IA 52242, USA.
Tel: +1 319 356 3168; e-mail: jack-stapleton@uiowa.edu
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Switching from TAF to TDF improves lipid profile and protects from weight gain

- Design: A retrospective chart review.
- 146 TAF-to-TDF switch (Switch group) were compared with 146 patients matched for sex, age, and third antiretroviral agent class who continued unchanged TAF-containing regimen (Control group).
- Data were collected at approximately 1 year (follow-up FU-1) and 2 years (follow-up FU-2) after baseline values.

	Switch group ($n = 146$)	Control group ($n = 146$)	P value
Male, *n* (%)	115 (79%)	115 (79%)	1.0
Age (years)	50 (9.6)	55 (9.6)	**<0.001**
Ethnicity, *n* (%)			1.0
Caucasian	132 (90%)	132 (90%)	
Black	8 (6%)	8 (6%)	
Asian	6 (4%)	6 (4%)	
Body weight (kg)	82.4 (18.4)	83.2 (17.7)	0.732
Body mass index (kg/m^2)	26.3 (5.0)	26.9 (5.0)	0.387
Current smokers, *n* (%)	49 (34%)	41 (28%)	0.128
Lipid-lowering agents, *n* (%)	28 (19%)	32 (22%)	0.671
Diabetes medication, *n* (%)	2 (1%)	9 (6%)	0.250
Hypertension medication, *n* (%)	42 (29%)	47 (32%)	0.525

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. The groups were matched for sex, age (±10 years), ethnicity, and third ART class. Data are given as mean (standard deviation).

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Switching from TAF to TDF improves lipid profile and protects from weight gain

	Switch group ($n = 146$)	Control group ($n = 146$)	P value
HIV transmission mode, *n* (%)			0.103
Male-to-male sexual contact	84 (58%)	70 (48%)	
Heterosexual contact	48 (33%)	60 (41%)	
Intravenous drug use	10 (7%)	6 (4%)	
Other/unknown	4 (3%)	10 (7%)	
Time since HIV diagnosis (years)	12 (7.0)	11 (6.3)	0.114
Total duration of ART (years)	9.5 (5.8)	8.5 (5.0)	0.129
Third ART class, *n* (%)			1.0
Participants taking INSTI	104 (71%)	104 (71%)	
Participants taking NNRTI	30 (21%)	30 (21%)	
Participants taking PI	11 (8%)	11 (8%)	
Participants taking NNRTI + INSTI	1 (1%)	1 (1%)	
Boosting agent, *n* (%)			**<0.001**
Cobicistat	2 (1%)	26 (18%)	
Ritonavir	9 (6%)	10 (7%)	
Single tablet users, *n* (%)	9 (6%)	64 (44%)	**<0.001**
$CD4^+$ cell count (10^6/l)	703 (301)	728 (278)	0.448
HIV-1 RNA, *n* (%)			1.0
Participants with <50 copies/ml	138 (94%)	138 (94%)	
Participants with 50–400 copies/ml	7 (5%)	7 (5%)	
Participants with >400 copies/mL	1 (1%)	1 (1%)	

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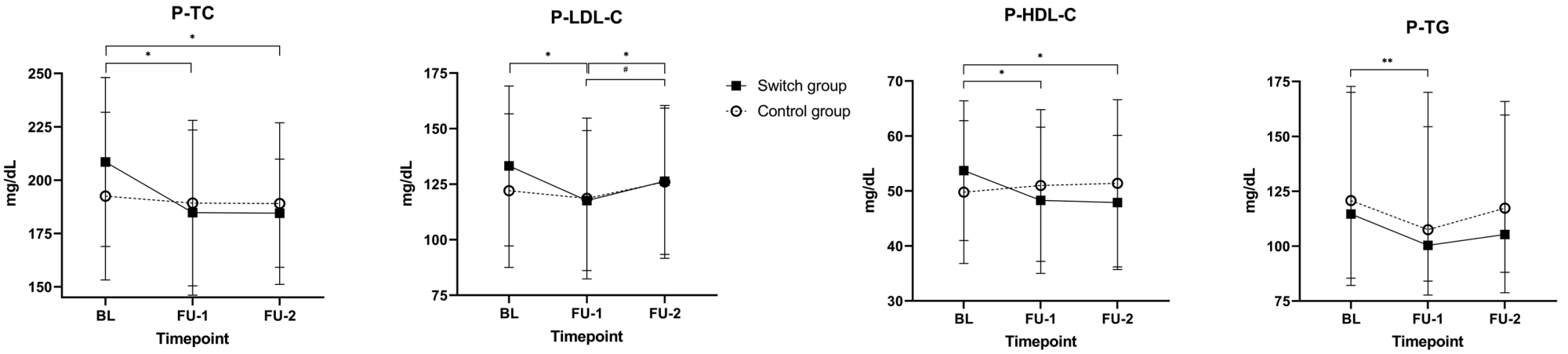
Switching from TAF to TDF improves lipid profile and protects from weight gain



	Switch group BL	Switch group FU-1	*P* value*	Control group BL	Control group FU-1	*P* value#
P-TC (mg/dl)	203.1 (41.7)	181.5 (40.0)	**<0.001**	195.1 (42.1)	194.5 (41.5)	0.816
P-LDL-C (mg/dl)	130.0 (35.9)	117.4 (32.2)	**<0.001**	124.4 (35.8)	123.1 (36.6)	0.512
P-HDL-C (mg/dl)	52.3 (13.2)	47.7 (14.0)	**<0.001**	51.4 (14.6)	52.8 (14.9)	0.083
P-TG (mg/dl), median (IQR)	109.8 (81.5 – 168.9)	101.9 (77.1–147.9)	**<0.001**	115.1 (83.3 – 167.6)	105.8 (82.6 – 158.3)	0.338
TC/HDL-C ratio, median (IQR)	3.8 (3.3–4.8)	3.8 (3.2–4.6)	0.401	3.8 (3.2–4.6)	3.7 (3.0–4.6)	0.208
P-Cr (mg/dl)	0.919 (0.154)	0.929 (0.164)	0.415	0.981 (0.216)	0.966 (0.219)	0.943
eGFR (ml/min)	93.5 (15.4)	92.0 (16.2)	0.172	85.3 (17.5)	85.5 (18.3)	0.452
P-Pi (mg/dl)	2.7 (0.6)	2.7 (0.5)	0.876	2.7 (0.6)	2.7 (0.6)	0.848
U-Prot (mg/l), median (IQR)	71.0 (67.0–98.0)	81.0 (67.0–128.0)	**0.022**	79.5 (67.0–121.0)	83.5 (67.0–140.0)	0.696
P-ALT (U/l), median (IQR)	28.0 (21.8–40.0)	31.0 (23.0–46.5)	**<0.001**	30.0 (21.0–42.0)	29.0 (19.0–39.0)	0.529
P-ALP (U/l), median (IQR)	70.0 (59.3–84.0)	78.5 (65.0–99.8)	**<0.001**	67.0 (54.0–81.5)	68.0 (55.0–82.0)	0.692
P-Gluc (mg/dl), median (IQR)	104.5 (97.3–112.2)	104.5 (99.1–111.7)	0.220	102.7 (95.5–114.0)	104.5 (97.3–117.1)	0.832

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Switching from TAF to TDF improves lipid profile and protects from weight gain

- During the study period, lipid lowering medication was started for 11 patients in Switch group and for 17 patients in Control group (P=0.191).
- In ASCVD risk analysis, the groups were not statistically significantly different at BL (P=0.116).
  - **The median (IQR) risk score decreased from 6.3% (2.4–11.5) at baseline to 6.0% (3.2 – 11.4) at FU-2, P=0.012, in switch group** and increased from 8.4% (3.0 – 14.8) to 9.1% (4.6 – 15.6), P=0.162, respectively

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

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

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. Data are given as mean (standard deviation).
*P-value for the pairwise comparison between BL and FU-1/FU-2 within the study group.
[a]P-value for the comparison between Switch and Control group at Baseline was $P=0.686$.
[b]P-value for the comparison between Switch and Control group at Baseline was $P=0.922$.

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EDITED BY
Filippo Giorgio Di Girolamo,
University of Trieste, Italy

REVIEWED BY
Ajibola Abioye,
Avicenna Research and Insights Center, Nigeria
Meghit Boumediene Khaled,
University of Sidi-Bel-Abbès, Algeria

*CORRESPONDENCE
Alvina Widhani
alvina.widhani@gmail.com

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Ramadan fasting reduces high-sensitivity C-reactive protein among HIV-infected patients receiving antiretroviral therapy

Alvina Widhani[1,2]*, Evy Yunihastuti[1,2], Siti Setiati[3,4], Fiastuti Witjaksono[5] and Teguh H. Karjadi[1,2]

[1]Allergy and Clinical Immunology Division, Department of Internal Medicine, Faculty of Medicine, Dr. Cipto Mangunkusumo General Hospital, Universitas Indonesia, Central Jakarta, Jakarta, Indonesia, [2]HIV Integrated Clinic, Dr. Cipto Mangunkusumo General Hospital, Central Jakarta, Jakarta, Indonesia, [3]Geriatric Division, Department of Internal Medicine, Faculty of Medicine, Dr. Cipto Mangunkusumo General Hospital, Universitas Indonesia, Central Jakarta, Jakarta, Indonesia, [4]Center for Clinical Epidemiology and Evidence Based Medicine, Faculty of Medicine, Dr. Cipto Mangunkusumo General Hospital, Universitas Indonesia, Central Jakarta, Jakarta, Indonesia, [5]Department of Clinical Nutrition, Faculty of Medicine, Dr. Cipto Mangunkusumo General Hospital, Universitas Indonesia, Central Jakarta, Jakarta, Indonesia

Background: Inflammatory conditions and oxidative stress increase in HIV infection, and inflammation increases the risk of cardiovascular disease. Ramadan fasting is known to reduce inflammation and oxidative stress in diabetic patients. This study examined the effects of Ramadan fasting on high-sensitivity C-reactive protein (hs-CRP) levels and total antioxidant status (TAOS) in HIV patients on antiretroviral therapy (ART).

Methods: This was a prospective cohort study comparing HIV-infected patients on stable ART who fasted throughout Ramadan to HIV-infected patients who did not fast during Ramadan. Inclusion criteria were men aged 20–40 years, taking first-line ART for at least 6 months, Muslims intent to fast for Ramadan, no current hospitalization because of acute conditions and not being treated for opportunistic infections.

Results: After 2 weeks, hs-CRP had decreased significantly in the fasting group (−0.41 mg/L [IQR = −1; 0.10]) compared to the non-fasting group (0.20 mg/L [IQR = −0.30; 1.50]) (p = 0.004). The linear regression analysis has shown that Ramadan fasting contributed to 10.10% of the variance in hs-CRP value (R^2 = 0.101) and decreased its value by 0.317 points (B = −0.317). Changes in TAOS did not significantly different (p = 0.405) between the fasting group (0.05 mmol/L [IQR = −0.03; 0.12]) and the non-fasting group (0.04 mmol/L [IQR = −0.13; 0.36]). In the fasting group, there were

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