Associations between inflammatory profiles and cardiovascular disease risk among people living with HIV

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POPPY
Pharmacokinetic and clinical observations in people over 50

BACKGROUND

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in people with HIV, even in those with suppressed HIV RNA levels [1].

CVD risk prediction algorithms, including QRISK, Framingham Risk Score (FRS), and the HIV-specific Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) score, can inform preventive therapies to mitigate CVD burden among people with HIV.

HIV-related factors such as persistent inflammation and immune activation have been hypothesized to play a role in the excess CVD risk observed among people with HIV compared to HIV-negative individuals [2]. However, the associations between inflammatory pathways and CVD risk among people with HIV are not clearly understood.

Aim: To assess the associations between inflammatory profiles and CVD risk among participants enrolled in the Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) Study.

METHODS

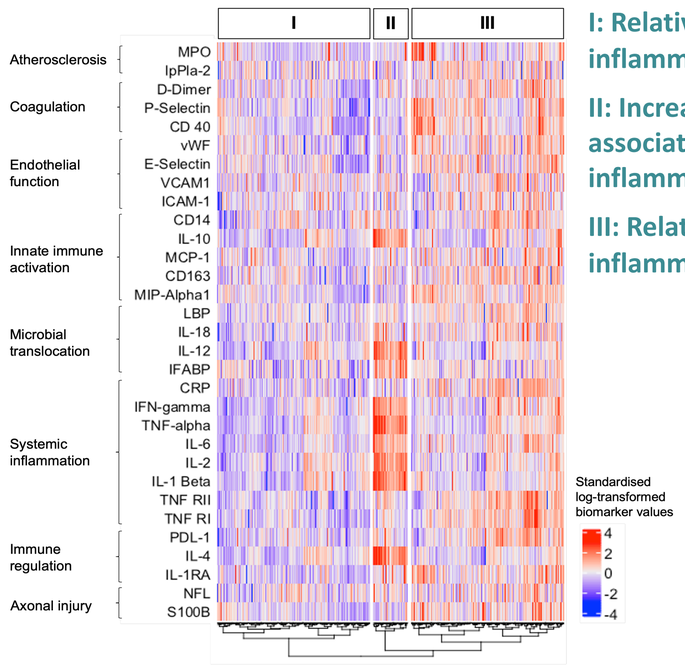
STUDY POPULATION

The POPPY study is a prospective, observational study that aims to examine the clinical outcomes of people with HIV from 7 sites in the UK and 1 in Ireland [3]. Information on sociodemographic, clinical, and lifestyle characteristics were collected from three cohorts: 699 aged ≥50 years with HIV, 374 aged <50 years with HIV, and 304 matched HIV-negative controls aged ≥50 years.

INFLAMMATORY PROFILES

Thirty-one biomarkers, related to a range of inflammatory pathways, were assessed using principal component analysis and hierarchical agglomerative cluster analysis in a subset of 465 participants with reliable biomarker data. Three distinct inflammatory clusters/profiles were identified (Figure 1).

Figure 1. Heatmap illustrating the three inflammatory profiles generated using thirty-one biomarkers and agglomerative clustering methods



I: Relatively low-levels of inflammation

II: Increased markers associated with systemic inflammation

III: Relatively high levels of inflammation

10-YEAR CVD RISK ALGORITHMS

The following predictors were included in the FRS, QRISK, and D:A:D algorithms:

Algorithm	Predictors
FRS	Age, sex, smoking, systolic blood pressure, antihypertensive drug use, total cholesterol, HDL cholesterol, and diabetes
QRISK	FRS predictors and ethnicity, CVD family history, body mass index (BMI), deprivation, chronic kidney disease, rheumatoid arthritis, and atrial fibrillation
D:A:D	FRS predictors and CVD family history, current CD4 cell count, current abacavir use, cumulative protease inhibitor and nucleoside reverse transcriptase inhibitor exposure.

10-year CVD risk scores were divided into categories: low (<10%), moderate (10-20%), and high (≥20%) risk scores.

STATISTICAL ANALYSES

The current analysis was limited to 312 participants who had complete data on all three CVD risk scores.

Quantile regression was applied to compare the distributions of 10-year CVD risk scores in those with different inflammatory profiles. All models adjusted for statin use. The FRS and D:A:D models also adjusted for race and BMI. The D:A:D model further adjusted for years infected with HIV, nadir CD4 count, duration of ART, and viral load.

ACKNOWLEDGEMENTS

POPPY Management Team: Marta Boffito, Paddy Mallon, Frank Post, Caroline Sabin, Memory Sachikonye, Alan Winston, Amalia Ndoutoumou, Daphne Babalis **POPPY Scientific Steering Committee:** Jane Anderson, David Asboe, Marta Boffito, Lucy Garvey, Paddy Mallon, Frank Post, Anton Pozniak, Caroline Sabin, Memory Sachikonye, Jaime Vera, Ian Williams, Alan Winston **POPPY-Sleep Management Team:** Ken Kunisaki, Susan Redline, Alan Winston, Caroline Sabin, Paddy Mallon, Nicki Doyle, Amalia Ndoutoumou **POPPY-Sleep Sleep Reading Centre Team:** Emily Kaplan, Dan Mobley, Michael Rueschman, Michelle Reid (Brigham and Women's Hospital, Boston/USA). **POPPY Sites and Trials Unit:** Caldecot Centre, King's College Hospital (Frank Post, Lucy Campbell, Selin Yurdakul, Sara Okumu, Louise Pollard, Beatriz Santana Suárez) Department of Infection and Population Health, UCL (Ian Williams, Damilola Otiko, Laura Phillips, Rosanna Laverick, Michelle Beynon, Anna-Lena Salz, Abigail Severn) Elton John Centre, Brighton and Sussex University Hospital (Martin Fisher, Amanda Clarke, Jaime Vera, Andrew Bexley, Celia Richardson, Sarah Kirk, Rebecca Gleig) Centre for Experimental Pathogen Host Research, School of Medicine, University College Dublin (Paddy Mallon, Alan Macken, Bijan Ghavani-Kia, Joanne Maher, Maria Byrne, Ailbhe Flaherty, Aoife McDermott, Riya Negi, Alejandro Garcia-Leon) Homerton Sexual Health Services, Homerton University Hospital (Jane Anderson, Sifiso Mguni, Rebecca Clark, Rhiannon Nevin-Dolan, Sambasivarao Pelluri) Ian Charleson Day Centre, Royal Free Hospital (Margaret Johnson, Nnenna Ngwu, Nargis Hemat, Anne Carroll, Sabine Kinloch, Mike Youle and Sara Madge) Imperial Clinical Trials Unit, Imperial College London (Daphne Babalis, Jodi Meyerowitz, Christina Prechtl) St. Mary's Hospital London, Imperial College Healthcare NHS Trust (Alan Winston, Lucy Garvey, Merle Henderson, Claire Peterson, Wilbert Ayap, Allan Lisenco) St Stephen's Centre, Chelsea and Westminster Hospital (Marta Boffito, David Asboe, Anton Pozniak, Margherita Bracchi, Nicole Pagani, Maddalena Cerrone, Daniel Bradshaw, Francesca Ferretti, Chris Higgs, Elisha Seah, Stephen Fletcher, Michelle Anthonipillai, Ashley Moyes, Katie Deats, Irtiza Syed, Clive Matthews, Peter Fernando) **POPPY methodology/statistics:** Caroline Sabin, Nicholas Bakewell, Hajra Okhai, Luxsena Sukumaran **Funders:** The POPPY Sleep Substudy (which these analyses were conducted for) was funded by National Heart Lung and Blood Institute (R01 HL131049). The parent POPPY Study is primarily funded by investigator-initiated grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare. We acknowledge the use of the National Institute for Health Research (NIHR)/Wellcome Trust Clinical Research Facility at King's College Hospital. The research is also funded by the National Institute for Health Research Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. This material is also the result of work supported with resources and the use of facilities at the Minneapolis Veterans Affairs Medical Center, Minneapolis, USA.

RESULTS

BASELINE CHARACTERISTICS

- The analyses included 312 participants (median [interquartile range; IQR] age 55 [51–60] years; 82% male; 91% white; median BMI 25.6 [23.1-28.4]). Of these 146 (47%), 36 (12%) and 130 (42%) participants were in clusters I, II and III, respectively.
- People with HIV were characterised by higher statin use (21%) and current smokers (28%) compared to people without HIV (13% and 16%, respectively). People without HIV included a greater proportion of people with diabetes (22%), a higher median total cholesterol (5.4 [4.6 – 6.0]) and BMI (26.2 [24.1 - 29.2]), compared to people with HIV (20%; 4.9 [4.2 – 5.5]; and 25.1 [22.9 - 28.2], respectively).

Table 1. Demographic, lifestyle, and clinical factors of included participants, overall and stratified by cluster

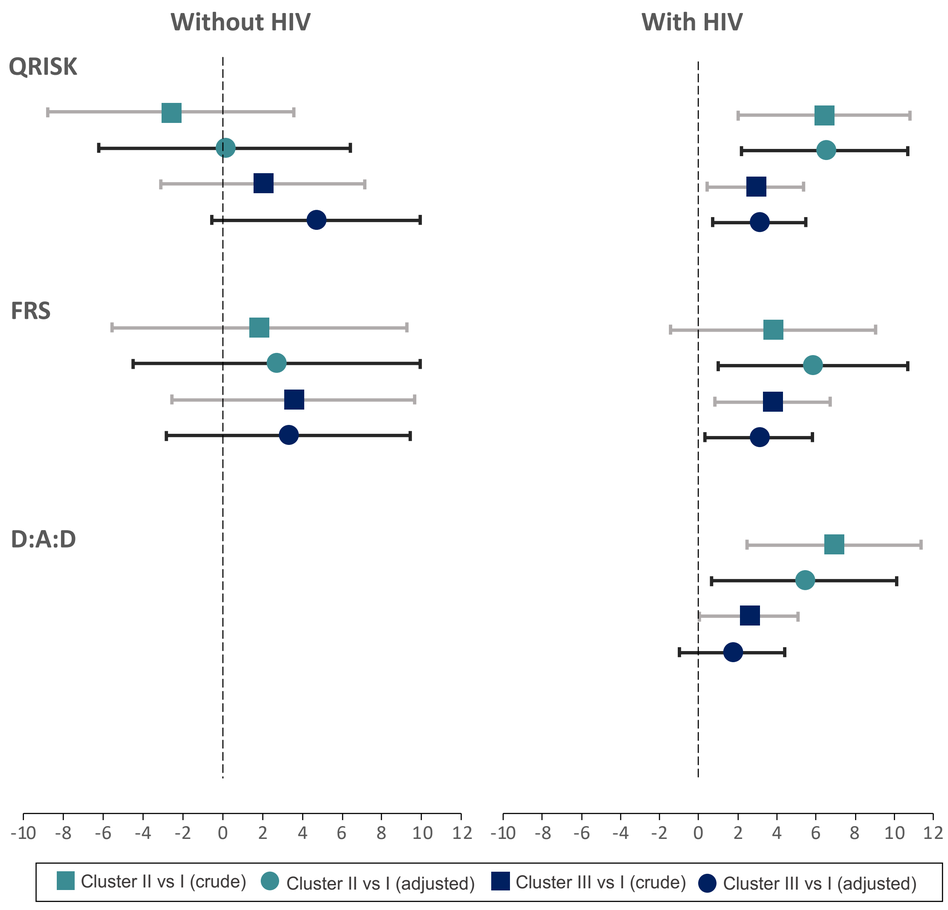
Characteristic n (%) or median (IQR)	**Total cohort (n=312)**	**Cluster I (n=146)**	**Cluster II (n=36)**	**Cluster III (n=130)**
People with HIV	218 (70)	99 (68)	19 (53)	100 (77)
Demographic factors				
Age, years	55 (51 - 60)	55 (50 - 60)	57 (52 - 62)	55 (51 - 60)
Male	258 (82.3)	119 (81.5)	27 (75)	112 (86.2)
White	285 (91.4)	135 (92.5)	32 (88.9)	118 (90.8)
Cardiovascular risk factors				
Statin use	58 (18.6)	27 (18.5)	3 (8.3)	28 (21.5)
Diabetes mellitus	65 (20.8)	31 (21.2)	10 (27.8)	24 (18.5)
Systolic blood pressure, mmHg	126 (116 - 140)	126 (116 – 136)	134 (125 - 154)	126 (115 - 140)
Total cholesterol, mg/dL	5 (4.3 - 5.7)	5 (4.3 - 5.7)	4.9 (4.2 – 5.6)	5.1 (4.4 – 5.7)
HDL cholesterol, mg/dL	1.3 (1.1 - 1.6)	1.3 (1.1 – 1.6)	1.4 (1.1 – 1.6)	1.3 (1.1 – 1.5)
Body mass index, kg/m^2	25.6 (23.1 - 28.4)	24.8 (22.5 - 27.3)	25.8 (24 – 29.1)	26.4 (23.7 – 29.7)
Smoking				
Never	130 (41.7)	62 (42.5)	17 (47.2)	51 (39.2)
Former	106 (34.0)	57 (39.0)	10 (27.8)	39 (30.0)
Current	76 (24.4)	27 (18.5)	9 (25.0)	30.8 (40)
HIV-related factors				
Years since HIV diagnosis	16.1 (8.2 – 21.9)	13.9 (7.7 – 21.7)	13.0 (8.2 – 18.0)	17.3 (9.6 – 22.6)
CD4 count, cells/µL	607.5 (468 – 756)	597 (472 – 760)	656 (460 – 792)	606 (458 – 750)
Nadir CD4 count, cells/µL	180 (99 - 280)	218 (120 – 302)	160 (108– 250)	143 (75 – 250)
HIV RNA undetectable (<50 copies/mL)	204 (93.6)	95 (96.0)	16 (84.2)	93 (93.0)
ART duration, years	10.3 (5.4 - 17.1)	8.5 (4.4 – 15.6)	12.6 (7.1 – 16.7)	11.7 (5.9 – 17.6)

ASSOCIATION BETWEEN INFLAMMATORY PROFILES AND CVD RISK

- Overall, the median [IQR] QRISK, FRS and D:A:D scores were 9.5% [5.0 - 15.7], 11.8% [6.8 - 18.7], and 9.0% [5.0 - 14.7], respectively. Cluster II and III included a higher proportion of people with high CVD risk compared to cluster I (Figure 2). Cluster III also included a higher proportion of people with moderate CVD risk compared to cluster I.
- Median FRS and QRISK scores for people without HIV were not statistically associated with cluster membership prior to or after adjustment of relevant covariates (Figure 3).
- Unadjusted quantile regression demonstrated statistically significant differences between the distributions of scores in the three cluster groups among people with HIV. After adjustment, both QRISK and FRS scores for people with HIV in cluster III were 3.1% higher compared to those in cluster I. Median [95% confidence intervals (CIs)] QRISK and FRS scores were significantly higher among those in cluster II compared to cluster I (QRISK: 6.5%; [2.21 -10.69] and FRS: 5.8%; [1.01 - 10.67]) after adjustment.
- Median [95% CIs] D:A:D scores were only significantly associated with cluster II, compared to cluster I, after adjustment (before: 6.9% [2.5 - 11.4]; after: 5.4% [0.7 - 10.2]).

Figure 2. Proportion of participants within each inflammatory profile by CVD risk category: **(a)** QRISK, **(b)** FRS, and **(c)** D:A:D score

Figure 3. Median (95% CIs) quantile models highlighting the associations between the inflammatory profiles and CVD risk, stratified by HIV status



*Reference group: cluster I (relatively low levels of inflammation)

CONCLUSION

Our work underscores the heterogeneity in CVD risk among people with HIV with different inflammatory profiles, thus suggesting the need for more tailored and detailed descriptions of CVD risk among distinct subgroups of people with HIV.

Our cross-sectional analysis was limited to assessing current, rather than incident, CVD risk. Thus, longitudinal analyses are needed to assess temporal relationships between inflammatory pathways and future CVD events among people with HIV. Furthermore, our findings should be interpreted with caution as our analysis includes individuals who reported a prior CVD event at baseline.

References: [1] Islam FM, *et al.* HIV Med 2012;13(8):453-68; [2]Duprez DA, *et al.* PLoS One 2012;7(9):e44454.; [3]Bagkeris E, *et al.* *Int J Epidemiol* 2018;47:1391-1392e