Associations between cytomegalovirus IgG concentrations and multimorbidity burden in people with HIV

Luxsena Sukumaran[1], Moises Alberto Suarez-Zdunek[2], Susanne Dam Nielsen[2], Nikolai Søren Kirkby[3], Fiona Burns[1], Jane Anderson[4], Marta Boffito[5], Jaime Vera[6], Nicki Doyle[7], Patrick WG Mallon[8], Frank A Post[9], Alan Winston[7], Caroline A Sabin[1]

[1]Institute for Global Health, UCL, London, United Kingdom; [2]Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark; [3]Department of Clinical Microbiology, Rigshospitalet, University of Copenhagen, Denmark; [4]Homerton University Hospital NHS Trust, United Kingdom; [5]Chelsea & Westminster Hospital NHS Foundation Trust, London, United Kingdom; [6]Brighton and Sussex Medical School, Brighton and Hove, United Kingdom; [7]Imperial College London, London, United Kingdom; [8]HIV Molecular Research Group, School of Medicine, University College Dublin, Dublin, Ireland; [9]King's College London, London, United Kingdom

BACKGROUND

Multimorbidity is increasingly common among people with HIV on antiretroviral therapy (ART) and may be driven by persistent immune activation [1]. Cytomegalovirus (CMV) infection is highly prevalent in this population and has been linked to systemic inflammation and non-AID related comorbidity [2]. We hypothesised that higher CMV IgG concentrations, reflecting CMV burden, is associated with greater multimorbidity burden among adults with HIV in the Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) cohort.

METHODS

STUDY POPULATION

The POPPY study collects data on sociodemographic, lifestyle and clinical characteristics from three groups: 699 people with HIV aged ≥50 years, 374 people with HIV aged <50 years, and 304 people without HIV aged ≥50 years [3].

CMV IgG CONCENTRATIONS

CMV IgG concentrations were measured in POPPY participants at baseline (April 2013-January 2016; DiaSorin LIAISON CMV IgG II).

MORBIDITY BURDEN Z-SCORES

Principal component analysis (PCA) identified five multimorbidity patterns in all participants with HIV at baseline (Table 1).

Table 1. Five multimorbidity patterns identified among all POPPY participants with HIV, with PCA loadings provided for comorbidities highly correlated with each pattern

Category	Comorbidities with PCA loading ≥0.25 with the category
CVDs	CABG/PTCA (0.68), Heart failure (0.62), Hypertension (0.70), IHD (0.72), Myocardial infarction (0.69), Peripheral vascular disease (0.46), Renal problems (0.40), Dyslipidemia (0.34)
Metabolic	Peripheral neuropathy (0.57), Type II diabetes (0.57), Hypothyroidism (0.46) Dyslipidemia (0.45), Pruritis (0.41), Prostate dysfunction (0.31), KS (0.30), PCP (0.30), CMV (0.28), Eye problems (0.26), Hepatitis B (0.26), Skin cancer (0.26), Urinary incontinence (0.25)
Mental/Joint	Clinical depression (0.75), Anxiety/Panic attacks (0.50), Joint inflammation/ Arthritis (0.45), Joint replacement (0.45), Sleeping problems (0.39), Bowel disorders (0.39), Asthma (0.34), Lipodystrophy (0.34), Eczema (0.28), Gastrointestinal reflux (0.27), Hypogonadism (0.25)
Neurological	Dizziness/Vertigo (0.61), Encephalitis (0.60), Loss of consciousness (0.39), Pruritus (0.32), Other AIDS (0.28), Migraines/headaches (0.28), Psychosis (0.27), Aches and Pains (0.27)
Cancer/Other	Haematological cancer (0.64), Hernia (0.45), Osteopenia/osteoporosis (0.44), AIDS-related cancer (0.43), PCP (0.32), CMV (0.29), PVD (0.28), DVT (0.27), HSV (0.26), Other AIDS (0.25)

CVD; Cardiovascular disease, CABG/PCTA; Coronary artery bypass/Percutaneous transluminal coronary angioplasty, MI; Myocardial infarction, IHD; Ischemic heart disease, STD; Sexually transmitted diseases, LGV; Lymphogranuloma venereum, HSV; Herpes simplex virus, PCP; Pneumocystis pneumonia, KS; Kaposi Sarcoma, CMV; Cytomegalovirus, PVD; Peripheral vascular disease, DVT; Deep vein thrombosis

Morbidity burden z-scores were calculated for each participant/pattern at baseline and follow-up (May 2015-February 2018) using PCA loadings applied to the presence or absence of correlated comorbidities (Table 1).

Scores were standardised with values >0 indicating higher burden relative to the baseline cohort mean. Change in burden was defined as the difference between visits.

STATISTICAL ANALYSIS

Associations between log-transformed CMV IgG and morbidity burden were assessed among CMV-seropositive participants using linear regression.

Model adjusted for age, sex, ethnicity, smoking status, alcohol use, recreational drug use, body mass index (BMI), years since HIV diagnosis, CD4+ count, nadir CD4+ and prior AIDS diagnosis.

Elevated CMV IgG is associated with greater mental/joint and cancer-related multimorbidity in people with HIV, highlighting CMV-driven immune activation as a potential risk pathway.

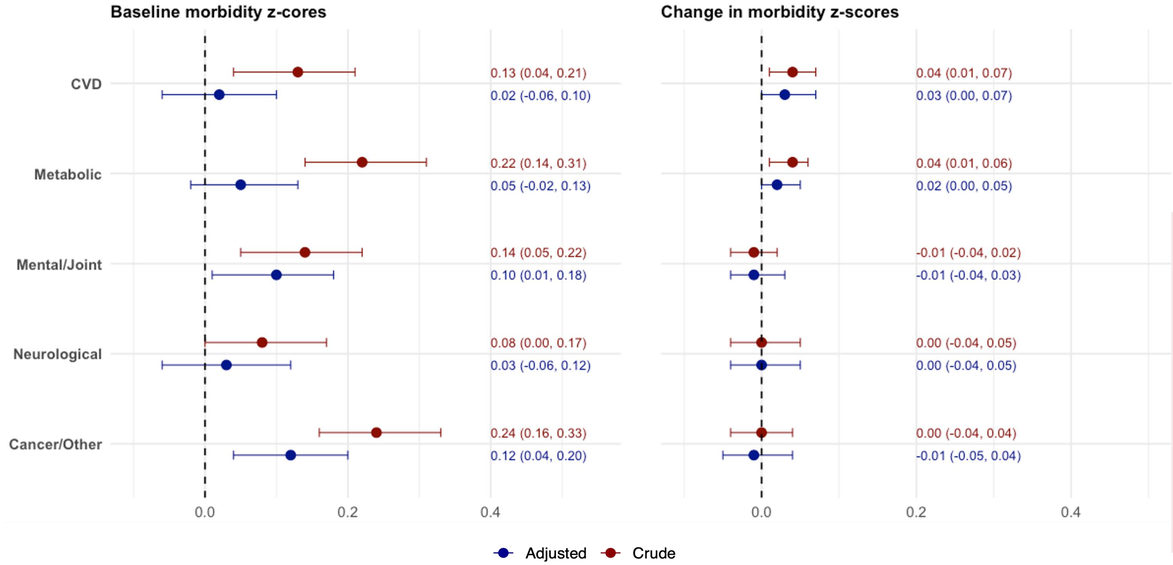
RESULTS

- Analyses included 720 CMV-seropositive participants with HIV (median [interquartile range; IQR] age 53 [48-59] years; 87% male; 85% White) (Table 2).
- At baseline, the median [IQR] z-scores were:
  - Metabolic: -0.30 (-0.89, 0.49)
  - Mental/Joint: -0.38 (-0.97, 0.68)
  - Neurological: -0.56 (-0.56, 0.32)
  - Cancer/Other: -0.62 (-0.62, 0.29)
  - CVD: -0.62 (-0.62, 0.56)
- In unadjusted analyses, higher CMV IgG was associated with greater CVD, Metabolic, Mental/Joint, and Cancer/Other burden.
- After adjustment, higher CMV IgG remained independently associated with greater Mental/Joint (β=0.10, p=0.03) and Cancer/Other burden (β=0.12, p=0.003).
- HIV-related parameters (years since HIV diagnosis and prior AIDS) were also strong independent predictors of burden.

Table 2. Baseline characteristics of study participants

Characteristic n (%) or median (IQR)	Total (n=720)
Age (years)	53 (48-59)
Gender	
Male	624 (86.7)
Female	96 (13.3)
Ethnicity	
Black-African	105 (14.6)
White	615 (85.4)
Sexual orientation	
MSM	569 (79.0)
Heterosexual	151 (21.0)
BMI	25.4 (23.2-28.0)
Smoking status	
Never	297 (41.3)
Past	250 (34.7)
Current	173 (24.0)
Recreational drug use	197 (27.4)
Alcohol use	
Never	58 (8.1)
Past	81 (11.3)
Current	581 (80.7)
HIV-specific clinical factors	
Years since HIV diagnosis	13.3 (7.7 - 20.4)
On ART	702 (97.5)
Current CD4+ count	626 (481-817)
Nadir CD4+ count	210 (108-320)
Prior AIDS event	211 (29.3)

Figure 1. Associations between log-transformed CMV IgG concentrations and morbidity z-scores among POPPY participants with HIV (n=720). Crude and adjusted beta estimates with 95% confidence intervals are shown.



CONCLUSIONS

- In this cohort of CMV-seropositive people with HIV, **higher CMV IgG concentrations were associated with greater Mental/Joint and Cancer-related** multimorbidity burden.
- CMV **IgG could potentially serve as a marker** to help identify individuals at **higher risk of multimorbidity** who may benefit from enhanced monitoring or tailored preventive strategies.
- **Future longitudinal and mechanistic studies** are needed to confirm these observations and explore whether interventions targeting CMV could reduce multimorbidity burden in people with HIV.

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PLAIN LANGUAGE SUMMARY

People with HIV may develop multiple health conditions as they age. Our study found that higher levels of cytomegalovirus (CMV) antibodies were linked to a greater burden of joint, mental health, and cancer-related conditions. Future work to see if knowing someone's CMV status can help identify those at higher risk for these health problems is warranted.