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Cohort Profile

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Cohort profile: The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) study

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Why was the cohort set up?

The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) Study was initiated in 2013 as the first large-scale study to assess clinical outcomes of people living with HIV (PLWH) over the age of 50 in England and Ireland. Discussions around the management of HIV as a chronic disease have been ongoing.[1–5] However, some recent studies have suggested a possible acceleration of the ageing process in PLWH, with reported increases in the rates of several comorbidities including cardiovascular disease (CVD), cancers, cognitive disorders, end-stage liver and renal diseases, and frailty and fracture risk.[6–10] The primary aims of the study are therefore: (i) to describe the burden of clinical conditions in older PLWH; ii) to investigate whether the burden of comorbidities is increased in PLWH compared with demographically similar HIV-negative people; and iii) to describe the outcomes of and resources required to treat some of the more common comorbidities expected to occur in older PLWH, to see whether these also appeared to differ between those with and without HIV. An additional, related, aim of the study is to investigate the impact of age on the concentrations of the different antiretroviral agents in the blood among PLWH. It is hoped that the study findings will contribute to the development and implementation of evidence-based recommendations for the optimal management and clinical monitoring of older PLWH. Study results will also contribute to the design of future studies for the treatment of diseases associated with ageing in this population. The study received ethical approval from the NHS Health Research Authority, National Research Ethics Service (NRES) Committee London. Ethics reference number is 12/LO/1409.

Who is in the cohort?

POPPY is a multicentre, prospective, observational study initially funded for three study visits which occur annually.

To address the primary aims of the study, three groups of individuals were invited to participate in the study: PLWH aged ≥50 years; PLWH aged <50 years; and a group of HIV-negative controls aged ≥50 years. All participants were of white or black African ethnicity and had acquired HIV via a sexual route (either sex between men or sex between men and women). Those recruited in the younger group of PLWH were frequency-matched to the group of older PLWH on gender, ethnicity, sexual orientation and participating clinic. HIV-negative participants were required to have a documented negative HIV test in the past 6 months or at the time of screening; this group was frequency-matched to the older PLWH group on age, gender, ethnicity, sexual orientation and geographical location (in or out of London).

Eight clinical sites currently participate in POPPY: Chelsea and Westminster Hospital (CWH), Homerton University Hospital (HUH), Kings College Hospital (KCH), Mortimer Market Centre (MMC), Royal Free Hospital (RFH), Royal Sussex County Hospital (RSH) and St Marys Hospital London (SMH) in England, and the Mater Misericordiae University Hospital, Dublin (DUH) in Ireland. Before recruitment, each centre was provided with recruitment targets (for age group, gender, race and route of HIV infection) based on the demographic characteristics of those attending each clinic, using data from the UK Collaborative HIV Cohort (UK CHIC) study[11] and the Dublin ID cohort,[12] to ensure that PLWH who participated in the study were broadly representative of PLWH in participating centres. The number of people to be recruited from each centre was agreed in advance with study investigators and was based on an agreed proportion of the total numbers of attenders at each clinic to ensure feasibility.

Identifying potential eligible participants and recruitment

Our goal was to recruit a study cohort that did not over-represent those who either attended clinic more frequently or who were more regular participants in research studies. To attempt to achieve this, each clinic's list of eligible attenders was ordered randomly, and clinics were asked to approach those at the top of the list first, before moving further down the list should insufficient numbers at the top of the list agree to participate. Although not a perfect approach, this was felt to be a recruitment method that would be feasible within a busy clinic setting.

Where possible, HIV-negative participants were selected from similar underlying populations (e.g. from genitourinary medicine clinics for the white men who have sex with men participants, and local community settings for those of black African origin).

The original planned sample size was 2000 (1000 older PLWH, 500 younger PLWH and 500 HIV-negative controls) and was chosen pragmatically to reflect what was thought to be feasible, given the number of people receiving care at each of the clinics. Given time constraints, however, recruitment was stopped once 1376 participants had been recruited (699 older PLWH, 374 younger PLWH and 304 HIV-negative controls) as it was thought that the additional effort that would be required to increase the sample size further would not be balanced by an increased amount of information in the cohort.

Characteristics of the cohort

The total cohort includes 1377 participants. Baseline demographic, clinical and lifestyle characteristics are shown in Table 1. In brief, 1109 (80.5%) of the cohort were male (88.0%, 80.8% and 64.0% in older PLWH, younger PLWH and HIV-negative controls, respectively), 963 (70.0%) define themselves as men who have sex with men (MSM) and 1175 (85.3%) have a white ethnic background. The median age is 56 [quartile (Q)1–Q3: 53–62] for the older PLWH, 43 (37–47) for the younger PLWH and 58 (53–63) for the HIV-negative controls, and almost 45% are single (54.0%, 31.0% and 15.0%, respectively). Finally, around two-thirds (64.7%) of participants are born to parents from the UK/Ireland.

To assess the representativeness of the older cohort (the younger cohort of PLWH was selected to be demographically similar to the older cohort, rather than to be representative of the UK HIV epidemic), we compared selected characteristics of the older cohort of PLWH within the UK POPPY sites ($n = 667/699$) with individuals attending the same clinics who would have been eligible for participation in the study (based on age, ethnicity and exposure group) at the start of 2013, but who were not included (n = 4786, Table 2). Information for the latter group was obtained from the UK CHIC study. Individuals who were included in POPPY were slightly more likely to be male (88.0% vs 85.4%), were more likely to report HIV infection through sex between men (79.8% vs 70.4%) and to be of white ethnicity (86.4% vs 79.5%) than non-participating individuals. The median age of the two groups was, however, similar (55 vs 54 years), as were the proportions of individuals exposed to antiretroviral therapy (ART) (90.9% vs 89.6%) and the median CD4 count on 1 January 2013 (590 cells/mm^3 in each group). Absolute differences in the viral load and nadir CD4 cell count between the two groups were small.

How often have they been followed up?

The current protocol entails the following study visits: a screening visit/visit 1 (baseline) conducted from April 2013

Table 1. Selected demographic, lifestyle and clinical characteristics of POPPY participants at study entry

	POPPY cohort		
	Older PLWH	Younger PLWH	HIV-negative
N	699	374	304
Visit 1 date	Apr 2013–Jan 2016	May 2013–Jan 2016	Apr 2013–Jan 2016
Gender, *n* (%)			
Male	612 (87.5)	302 (80.8)	195 (64.0)
Female	87 (12.5)	72 (19.3)	109 (36.0)
Mode of infection/sexuality[a], *n* (%)			
Men who have sex with men (MSM)	550 (78.7)	269 (71.9)	144 (47.4)
Heterosexual	149 (21.3)	105 (28.1)	160 (52.6)
Race, *n* (%)			
White	603 (86.3)	299 (80.2)	273 (90.0)
Black African	96 (13.7)	75 (19.8)	31 (10.0)
Age (years), median (Q1–Q3)	57 (53–62)	43 (37–47)	58 (53–63)
Marital status, *n* (%)			
Single	332 (47.5)	193 (51.6)	91 (29.9)
Married/in partnership	264 (37.8)	148 (39.6)	158 (52.0)
Other	103 (14.7)	33 (8.8)	55 (18.1)
Country of birth			
UK/Ireland	481 (68.8)	186 (50.0)	223 (13.0)
Africa	110 (15.7)	80 (20.8)	41 (13.3)
Other	108 (15.5)	108 (28.9)	40 (13.2)
BMI (kg/m^2), median (Q1–Q3)	26 (23–29)	25 (23–28)	27 (24–30)
Smoking status, n (%)			
Current	158 (22.6)	109 (29.2)	42 (13.8)
Ex-smoker	263 (37.7)	102 (27.3)	121 (39.8)
Never smoker	275 (39.3)	161 (43.1)	139 (45.7)
Unknown	3 (0.4)	2 (0.5)	2 (0.7)
Alcohol consumption, n (%)			
Current	555 (79.4)	303 (81.0)	262 (86.2)
Previous drinker	87 (12.5)	38 (10.2)	24 (7.9)
Never	57 (8.2)	33 (8.8)	18 (5.9)
Recreational drug use in previous 6 months, *n* (%)	177 (25.3)	130 (35.0)	44 (13.9)

[a]Mode of HIV infection for PLWH, self-reported sexuality for HIV-negative cohort.

until January 2016, during which eligibility criteria were confirmed and informed consent was taken; visit 2 (year 1) from May 2014 to February 2017; and visit 3 (year 2) from May 2015 to February 2018 (ongoing). Whereas the baseline and year 2 visits are conducted via face-to-face interviews for all participants, the intervening year 1 visit is only conducted face-to-face for the two groups of PLWH; the HIV-negative controls are contacted by phone for a brief follow-up assessment. Current funding applications are under consideration, to allow additional follow-up visits of the cohort.

At the time of writing this manuscript (August 2017), 1315 (95.5%) of the cohort have reached visit 2, and 508 (36.9%) have reached visit 3. Eleven of the study participants have died, 10 from the older group of PLWH and 1 from the HIV-negative cohort. Causes of death were: endocarditis, sepsis, ischaemic and hypertrophic heart disease, myocardial infarction, adenocarcinoma, suicide, heart attack, cardiac arrest, end-stage liver disease and angiosarcoma; 32 participants have withdrawn from further participation, 17 from the older PLWH cohort, 11 from the younger PLWH cohort and 4 from the HIV-negative cohort. The Imperial College Clinical Trials Unit (ICTU) makes efforts to retain a low attrition rate.

What has been measured?

A detailed schematic showing the information collected at each visit is shown in Table 3. At the baseline and year 2 visits, information is collected on demographics, socioeconomic status, anthropometrics and lifestyle factors. A full clinical history is taken by trained clinical research staff, with a particular focus on any comorbidities or clinical conditions that are present, any medications that have been received and any health care resources that have been used over the past year.

Table 2. Demographic and clinical characteristics (defined at 1 January 2013) of 698 PLWH aged ≥50 years from UK sites in the POPPY study, compared with eligible individuals from participating UK clinics who were not included in the study

	Eligible non-POPPY participants at participating clinics[a]	POPPY participants[b]	*P*-value
N	4786	667	
Male, *n* (%)	4086 (85.4)	587 (88.0)	0.08
Exposure group, *n* (%)			
Men who have sex with men (MSM)	3369 (70.4)	532 (79.8)	0.0001
Heterosexual	1417 (29.6)	135 (20.2)	
Ethnic origin, *n* (%)			
White	3806 (79.5)	576 (86.4)	0.0001
Black African	980 (20.5)	91 (13.6)	
Age (years) on 1 Jan 2013, median (Q1–Q3)	54 (52–60)	55 (51–60)	0.34
Exposed to ART, *n* (%)	4290 (89.6)	606 (90.9)	0.37
HIV RNA on 1 Jan 2013			
Median (Q1–Q3) $\log_{10}$ copies/ml	1.60 (1.60-1.70)	1.60 (1.60-1.70)	0.02
N (%) <50 copies/ml	3989 (89.7)	565 (91.7)	0.03
CD4 count on 1 Jan 2013 (cells/mm^3), median (Q1–Q3)	590 (430–779)	590 (432–780)	0.94
Nadir CD4 count on 1 Jan 2013 (cells/mm^3), median (Q1–Q3)	160 (70–254)	177 (84–270)	0.04

[a]Eligible non-POPPY participants were those who were under follow-up and aged ≥50 years at a participating site on 1 January 2013, who were of white or black African origin and infected with HIV through a sexual route. Information obtained through linkage with the UK CHIC study.

[b]Analysis of POPPY participants was restricted to UK POPPY sites only.

Table 3. Schematic description of the information captured through scheduled POPPY visits

	Screening	Baseline visit 1	Visit 2 (12 months after visit 1)[a]	Visit 3 (24 months after visit 1)
Informed consent	X			
Review eligibility	X	X		
Detailed medical history as per protocol		X	X	X
Study questionnaire		X	X	X
Cognitive assessment		X		X
DXA scan		X		X
Blood and urine sampling		X		X

[a]HIV-positive cohorts only; a brief assessment of the HIV-negative cohort at visit 2 is undertaken by phone.

Information on family history of clinical conditions is collected along with current and historical use of ART, for both the older and younger PLWH. Gender-specific information has been collected for pregnancies and screening for cervical and breast cancer for women, and anal cancer screening for men. Cognitive function is assessed at baseline and year 2, using specific memory and cognitive testing assessing cortical and sub-cortical function, and a detailed pain assessment reports regional and widespread pain using a validated mannequin. A full dual X-ray absorptiometry (DXA) scan is performed at baseline and year 2. Local scanners are used for measuring bone mineral density (BMD) to evaluate bone health and determine the likelihood of osteoporosis or bone fractures. To supplement this, information is also captured on any falls that the participant has experienced over the previous year, and on factors that will permit an assessment of falls and frailty risk.

Blood [serum, plasma and peripheral blood mononuclear cells (PBMC)] is taken for storage and for pharmacokinetic analysis at baseline and year 2; it is planned that this will be used for subsequent projects of the potential pathogenic mechanisms underlying age-related diseases. Plasma of 4–5 ml blood in ethylenediaminetetraacetic acid (EDTA) or lithium heparin has been collected for pharmacokinetic analysis, including but not limited to antiretroviral drug exposure and drug-drug interaction (DDI) of concomitant medication. For each participant, sample time. time of food intake nearest to the latest dose before sampling, and food content were recorded. PLWH also reported the time of latest ART dose. Other samples collected include 3 x 6 ml of

plasma in EDTA, 15 ml of serum and approximately 5 ml of urine.

Linkage to historical longitudinal HIV data

For participants at the UK sites, data linkage is performed with the UK CHIC study to provide access to historical longitudinal data on ART, hepatitis B virus (HBV) and hepatitis C virus (HCV) status and laboratory data including CD4 counts and percentages, CD8 counts and percentages and assessments of HIV RNA.[11] For participants at the Dublin site, historical longitudinal data were available through linkage with the Dublin ID cohort, which includes all patients diagnosed with HIV and seen for care at the Mater Misericordiae University Hospital in Dublin from 1993 to 1* December 2014.

What has been found? Key findings and publications

Given the broad subject information collected through the POPPY study, a long list of projects is involved, investigating the association of ageing with several comorbidities. Future ongoing and planned projects will involve studies of: sleeping patterns, muscle biopsy, pharmacokinetic and DDIs, cerebrovascular and cardiovascular disease, cognitive analysis, the menopause in women living with HIV, hepatic steatosis, respiratory events, bone health and fractures, mental health and chronic pain.

A recent project within POPPY investigated the agreement of different approaches used to define cognitive impairment in HIV.[13] The Frascati criteria, global deficit score (GDS) and multivariate normative comparison (MNC) were used to define cognitive impairment. We found that the different criteria of cognitive impairment show fair diagnostic agreement in PLWH and that those meeting all three criteria had the highest rates of symptomatology. In another POPPY publication, Underwood *et al.*[14] found weak associations between the same three criteria of cognitive impairment and patient-reported measures of physical/mental functioning in older PLWH.

What are the main strengths and weaknesses?

Currently, there is no large study on HIV and the effects of ageing in the UK and Ireland. Internationally, several research groups have developed initiatives in this area, but most of these studies are either limited by size or are still at the recruitment stage. POPPY is a large multicentre cohort and is representative of the HIV-positive population in the UK and Ireland, which achieved a remarkable enrolment of almost 1400 participants. The inclusion of an older cohort of PLWH, a younger cohort of PLWH and an appropriately selected older HIV-negative control group in the study allows for direct comparisons of clinical outcomes between the older PLWH and HIV-negative controls, and the inclusion of the younger cohort of PLWH elucidates the effect of age among PLWH.

The data linkage of POPPY with a well-established Irish HIV centre and centres that are already participating in the UK CHIC cohort, enabled the enhancement of the quality of the data and allowed access to HIV-specific historical data of the POPPY participants, minimizing the resources that are required to collect historical longitudinal HIV data. The cohort will be of help in determining a wide range of data over time, related to clinical outcomes and HIV and ageing, which will facilitate research that involves long-term follow-up. POPPY study is an important cohort for those investigating the mechanism of HIV and ageing, clinical conditions and the impact of ART in Ireland and UK.

Limitations of the POPPY study include the lack of a young HIV-negative group that would facilitate a direct comparison with the younger group of PLWH, and an overrepresentation of white women among the HIV-negative control group. Due to time and budget constraints, this was not feasible. Future studies should consider incorporating such a group in their design in order to understand patterns and behaviours as well as similarities and differences compared with younger PLWH.

Can I get hold of the data? Where can I find out more?

Further information for the cohort collaboration policy can be obtained from Professor Caroline A Sabin [c.sabin@ucl.ac.uk] and Professor Alan Winston [a.winston@imperial.ac.uk].

Profile in a nutshell

- The POPPY Study is the first large-scale study to assess clinical outcomes of people living with HIV (PLWH) over the age of 50 in England and Ireland.
- PLWH aged ≥50 years ($n = 699$), PLWH aged <50 years ($n = 374$) and HIV-negative people aged ≥50 years ($n = 304$), frequency-matched for demographics and lifestyle, were recruited from eight sites in the UK and Ireland. Study visits started in April 2013. The cohort is largely male (80.5%), men who have sex with men (MSM) (70.0%) and of White ethnicity (85.3%). The median age was 56 (first quartile-third quartile: 53–62), 43 (37–48) and 58 (54–63) in the three groups, respectively.
- Participants are seen annually; 586 of the cohort have attended all three currently funded visits, 11

participants have died and 32 have been lost to follow-up.
- Information is collected on demographics, socioeconomic status, anthropometrics and lifestyle factors. A clinical history is taken, and information is collected on medications and health care resources that have been used over the past year. Cognitive function, bone health and pain are assessed, and blood samples are stored. Data linkage is performed with two HIV cohort studies to provide access to historical longitudinal HIV data.
- Further information can be obtained from Prof. Caroline A Sabin [c.sabin@ucl.ac.uk] and Prof. Alan Winston [a.winston@imperial.ac.uk].

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