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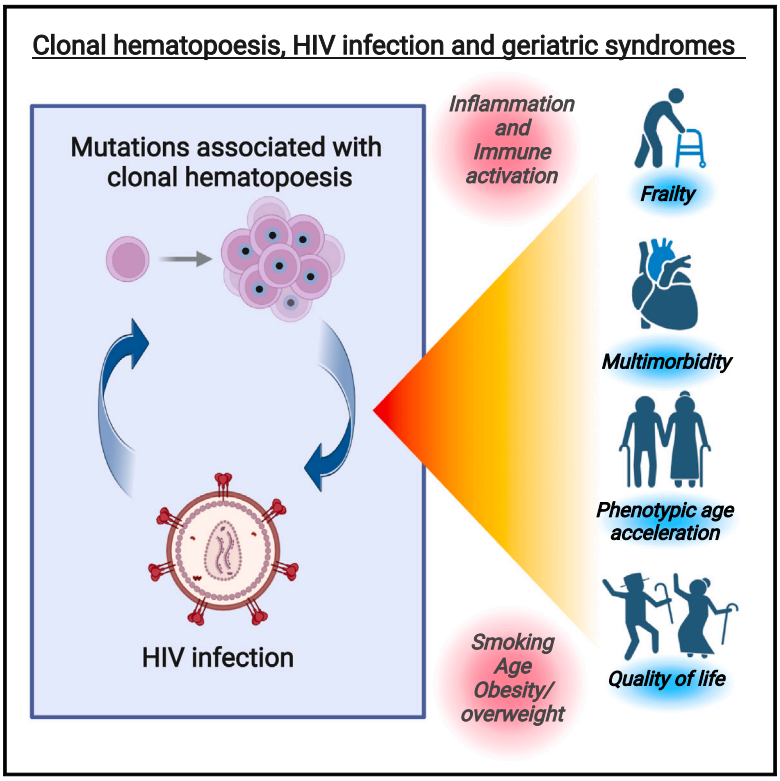
Age-related clonal hematopoiesis and HIV infection are associated with geriatric outcomes: The ARCHIVE study

Graphical abstract



Highlights

- We evaluate the associations of HIV and clonal hematopoiesis (CH) with geriatric syndromes
- HIV infection is associated with increased phenotypic age acceleration
- CH is independently associated with frailty and reduced quality of life
- CH may be used as a biomarker for adverse geriatric outcomes

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In brief

Han et al. examine the relationship between clonal hematopoiesis (CH), HIV, and geriatric syndromes in the ARCHIVE study, including adults with and without HIV. Findings suggest that HIV is associated with increased biological age, while CH may independently predict adverse geriatric outcomes, such as frailty and reduced quality of life.

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Report

Age-related clonal hematopoiesis and HIV infection are associated with geriatric outcomes: The ARCHIVE study

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SUMMARY

While HIV infection and clonal hematopoiesis (CH) have been linked with inflammatory dysregulation and an increased risk of aging-related comorbidities, their relationship with clinical geriatric syndromes has not been well defined. In the Age-related Clonal Haematopoiesis in an HIV Evaluation Cohort (ARCHIVE) study (NCT04641013), we measure associations between HIV and CH and geriatric syndromes. Of 345 participants (176 with HIV and 169 without HIV), 23% had at least one mutation associated with CH: 27% with HIV and 18% without HIV (p = 0.048). In adjusted analyses, HIV infection is independently associated with increased phenotypic age acceleration (coefficient 1.73, 95% confidence interval [CI] 0.3, 3.16) and CH is independently associated with being frail (vs. pre-frail/robust; odds ratio 2.38, 95% CI 1.01, 5.67) and with having reduced quality of life (coefficient −2.18, 95% CI −3.92, −0.44). Our findings suggest that HIV is associated with increased biological age and that CH may be used as a biomarker for adverse geriatric outcomes.

INTRODUCTION

The World Health Organization estimates that by 2050, the proportion of the global population over 60 years of age will nearly double from 12% in 2015 to 22%.[1] Recognizing this, the United Nations has proposed the Decade of Healthy Ageing 2020–2030,[2] a strategy that aims to not just add more years to life but to add more life to years. As a result, reducing the morbidity associated with aging-related comorbidities and geriatric syndromes and improving the quality

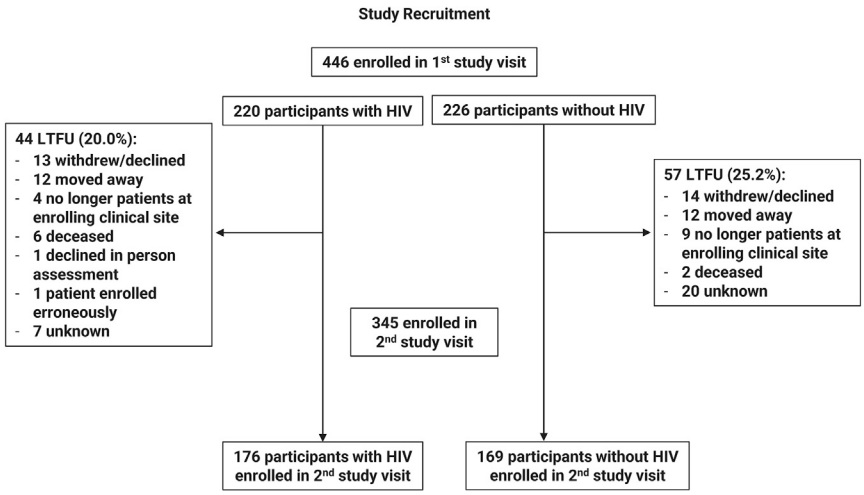

Figure 1. Study recruitment and loss to follow-up

of life, not just the number of years lived, is now a central focus of public health initiatives.

Chronic inflammation is both a consequence of aging and a key driver of adverse aging-related clinical outcomes. Inflammation is associated with geriatric syndromes such as frailty[3] and many high-burden medical comorbidities such as cardiovascular disease[4] and malignancies.[5] In recent years, research into clonal hematopoiesis (CH), the expansion of clonal populations of stem cells that is driven by certain somatic mutations that increase with age,[6,7] has demonstrated that the emergence and persistence of CH mutations are promoted in inflammatory environments and that the presence of CH mutations is associated with inflammation and aging- and inflammation-related comorbidities such as cardiovascular disease, malignancies, and mortality.[6,7]

Chronic HIV infection is also associated with inflammation[8] and with an increased risk of aging-related conditions such as frailty,[9,10] which is associated with negative health outcomes,[11] and medical comorbidities such as cardiovascular disease, stroke, malignancies, and rheumatologic diseases.[8,12–15] While the pathophysiology behind the increased risk of aging-related conditions and comorbidities in people with HIV is complex and certainly related to traditional risk factors such as smoking,[16–18] alcohol use,[16] dyslipidemia,[19] and hypertension,[20] HIV-specific factors such as side effects from antiretroviral therapy (ART)[21] and inflammatory dysregulation induced by chronic infection[8] are also thought to play a significant role.

In the Age-related Clonal Haematopoiesis in an HIV Evaluation Cohort (ARCHIVE) study,[22] we demonstrated that among adults >55 years of age, participants with HIV had over twice the risk of having CH compared to participants without HIV. In addition, we found an association between HIV, CH, and inflammatory biomarkers, suggesting that inflammation associated with chronic HIV infection may facilitate the emergence and persistence of CH. Other studies have also demonstrated the increased prevalence of CH in people with HIV[23,24] and have shown that CH is associated with lower CD4 nadir[25] and increased low-level HIV replication,[24] and, like the general population, associated with cardiovascular disease,[26] subclinical atherosclerosis,[23] and cancer.[27] Recent data on CH in people with HIV, especially individuals with a low CD4 nadir and a history of opportunistic infections and inflammatory syndromes, demonstrated that a history of inflammatory syndromes was associated with CH and that CH, in turn, was linked to dysregulated inflammation. Given the link between HIV and CH[22–24] and the known link between HIV and increased medical comorbidities[12] and frailty,[9] which are also driven by inflammation,[3,28–30] we evaluated participants in the ARCHIVE study to determine whether HIV or CH was associated with adverse aging-related clinical outcomes.

RESULTS

Of 446 participants who completed the ARCHIVE enrollment visit (2017–2018; 220 people living with HIV and 226 people without HIV), 345 completed the second study visit (2021–2022; 176 with HIV [51%] and 169 without HIV [49%]) and 101 were lost to follow-up (LTFU) (Figure 1). The median duration between the first and the second visit was 3 (interquartile range [IQR] 2.7–3.3) years. Demographic characteristics including age, gender, sexual orientation, and HIV status were generally comparable between those retained in the study and those LTFU. However, participants who were LTFU were less likely to have private insurance or a household annual income $\geq$ AUD$50,000, though there was a higher amount of missing data among those LTFU. Compared to those retained in the study, participants who were LTFU were also more likely to have been enrolled from tertiary care centers as opposed to primary care settings (Table S1).

Of the 345 participants who completed the second study visit, 96.8% were male, 88.7% were men who have sex with men, the median age was 67 (IQR 62, 72) years, 159 (46%) reported ever smoking, 294 (85%) reported ever drinking, and 81 (24%) had used a recreational drug in the past 12 months (Table 1). Of the 272 (79%) participants reporting having any comorbidity, 59 (17%) had diabetes mellitus and 185 (54%) had a composite cardiovascular disease event (any one of hypertension, myocardial infarction, congestive heart failure, angina, and stroke), with hypertension (47%) being the most common. From data collected at the first study visit, hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection was present in 23 (7%) and 24 (7%), respectively, and 79 (23%) had at least one CH mutation, 31 (18%) of the 169 without HIV and 48 (27%) of the 176 with HIV (p = 0.045); of those with any CH mutation, 21 (27%) had >1 mutation.

Among 176 participants with HIV, the median current CD4 count was 670 (IQR 482, 861) cells/mm^3, the median nadir

Table 1. Demographic and clinical characteristics of the study participants

	Total participants (N = 345)		*HIV negative (N = 169)*		*HIV positive (N = 176)*	
Characteristics	Number or Median	% or IQR	Number or Median	% or IQR	Number or Median	% or IQR
Median age (years)	67	62, 72	67	62, 73	67	63, 72
≤ 65	146	42.3	70	41.4	76	43.2
>65	199	57.7	99	58.6	100	56.8
Gender[a]						
Male	334	96.8	160	94.7	174	98.9
Female	11	3.2	9	5.3	2	1.1
BMI[a]	26	24, 29	26	24, 30	26	24, 28
<25 (underweight or normal weight)	131	38.0	64	37.9	67	38.1
≥25 (overweight or obese)	213	61.7	104	61.5	109	61.9
Missing	1	0.3	1	0.6	0	0
Sexual orientation[a]						
MSM	306	88.7	145	85.8	161	91.5
Other	30	8.7	19	11.2	11	6.3
Missing	9	2.6	5	3	4	2.3
Smoking						
Never smoked	151	43.8	80	47.3	71	40.3
Ever smoke	159	46.1	76	45.0	83	47.2
Missing	35	10.1	13	7.7	22	12.5
Drinking						
Never drank	16	4.6	6	3.6	10	5.7
Used to drink	53	15.4	31	18.3	22	12.5
Currently drink	241	69.9	119	70.4	122	69.3
Missing	35	10.1	13	7.7	22	12.5
Recreational drug use in past 12 months (at baseline)						
No	226	65.5	114	67.5	112	63.6
Yes	81	23.5	39	23.1	42	23.9
Missing	38	11.0	16	9.4	22	12.5
Injecting drug use in past 12 months (at baseline)						
No	296	85.8	150	88.8	146	82.9
Yes	9	2.6	4	2.4	5	2.9
Missing	40	11.6	15	8.9	25	14.2
Education level						
Secondary school or lower	97	28.1	47	27.8	50	28.6
Tertiary or higher	202	58.6	101	59.8	101	57.4
Missing	47	13.3	21	12.4	25	14.3
Employment status						
Working full time/part time	87	25.2	53	31.4	34	19.3
Not employed	211	61.2	95	56.2	116	65.9
Missing	47	13.6	21	12.4	26	14.8
Clinic type						
Primary care clinics	294	85.5	164	97.0	130	73.9
Tertiary care centers	51	14.9	5	3.0	46	26.1
Any CH mutation[a]						
No	266	77.1	138	81.7	128	72.7
Yes	79	22.9	31	18.3	48	27.3
CH mutation[a]						
No	266	77.1	138	81.7	128	72.7

(*Continued on next page*)

Table 1. *Continued*

Characteristics	*Total participants (N = 345)*		*HIV negative (N = 169)*		*HIV positive (N = 176)*	
	Number or Median	% or IQR	Number or Median	% or IQR	Number or Median	% or IQR
1 mutation	58	16.8	21	12.4	37	21.0
>1 mutation	21	6.1	10	5.9	11	6.3
Median VAF[c] for those with CH mutation (*n* = 79)	5.2	2.4, 8.0	5.2	2.3, 7.4	4.3	2.5, 7.2
Highest VAF[d] for those with CH mutation (*n* = 79)[a]	*n* = 79	–	*n* = 31	–	*n* = 48	–
VAF <5%	41	51.9	12	38.7	29	60.4
VAF ≥5%	38	48.1	19	61.3	19	39.6
Highest VAF[d] for those with CH mutation (*n* = 79)[a]	*n* = 79	–	*n* = 31	–	*n* = 48	–
VAF <10%	63	79.7	23	74.2	40	83.3
VAF ≥10%	16	20.3	8	25.8	8	16.7
Self-reported comorbidities						
Diabetes mellitus	59	17.1	28	16.6	31	17.6
Hypertension	163	47.3	73	43.2	90	21.1
Lung disease	66	19.2	35	20.7	31	17.7
Cancer	22	6.4	12	6.9	10	5.9
Heart attack	24	7	12	7.1	12	6.9
Congestive heart failure	10	2.9	6	3.6	4	2.3
Angina	16	4.6	9	5.3	7	4.0
Asthma	53	15.4	25	14.8	28	16
Arthritis	111	32.3	59	34.9	52	29.7
Stroke	23	6.7	8	4.7	15	8.6
Kidney disease	18	5.2	6	3.6	12	6.9
Composite CVD[b]						
No	159	46.2	83	49.1	76	43.3
Yes	185	53.8	86	50.9	99	56.6
HBV co-infection[a]						
No	321	93.0	161	95.3	160	90.9
Yes	24	7.0	8	4.7	16	9.1
HCV co-infection[a]						
No	321	93.0	159	94.0	162	92.0
Yes	24	7.0	10	6.0	14	8.0
Multimorbidity						
No	183	53.0	91	53.8	92	52.3
Yes	162	47.0	78	46.2	84	47.7
Frailty						
Robust	226	65.5	115	68.1	111	63.1
Pre-frail	95	27.5	43	25.4	52	29.5
Frail	24	7.0	11	6.5	13	7.4
PhenoAge (years), median (IQR)	68.3	62.7, 74.6	67.6	62.3, 73.5	68.6	63.6, 75.2
Missing	14	4	6	3.5	8	4.6
PhenoAge acceleration, median (IQR)	0.6	−2.5, 5.0	−0.2	−3.2, 4.0	1.9	−2.2, 6.3
Missing	14	4	6	3.5	8	4.6
Quality of Life score, median (IQR)	36	29, 39	36	32, 40	35	27, 39
Missing	64	18.6	32	18.9	32	18.3
Activities of Daily Living score, median (IQR)	20	20, 20	20	20, 20	20	20, 20

(*Continued on next page*)

Table 1. *Continued*

Characteristics	*Total participants (N = 345)*		*HIV negative (N = 169)*		*HIV positive (N = 176)*	
	Number or Median	% or IQR	Number or Median	% or IQR	Number or Median	% or IQR
Independent	224	64.9	114	67.5	110	62.5
Dependent in some way	57	16.5	23	13.6	34	19.3
Missing	64	18.6	32	18.9	32	18.2
Instrumental Activities of Daily Living score, median (IQR)	8	8, 8	8	8, 8	8	8, 8
Independent	232	67.3	118	69.8	114	64.8
Dependent in some way	59	17.1	25	14.8	34	19.3
Missing	54	15.7	26	15.4	28	15.9

BMI, body mass index; MSM, men who have sex with men; CH, clonal hematopoiesis; VAF, variant allele fraction; CVD, cardiovascular disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PhenoAge, phenotypic age; IQR, interquartile range.
[a]Data for gender, BMI, sexual orientation, CH mutation, VAF, hepatitis B, and hepatitis C virus infection were obtained at the first study visit.
[b]Composite cardiovascular disease endpoint consists of heart attack, congestive heart failure, angina, and stroke.
[c]The median VAF in participants who had more than one CH mutation was calculated by averaging the VAF values across all mutations for each participant.
[d]The highest VAF was the maximum VAF value observed among the mutations for each participant.

CD4 count was 248 (IQR 143, 372) cells/mm^3, the median duration of HIV and ART was 26.5 (IQR 18, 33) and 21 (13, 24) years, respectively, and 166 (94.3%) had HIV-1 RNA ≤40 copies/mL. Thirty-seven (21%) had a history of AIDS diagnosis (Table S2).

Geriatric outcomes: Frailty, multimorbidity, phenotypic age acceleration, and quality of life

Frailty

In total, 95 (27%) and 24 (7%) participants were pre-frail and frail, respectively (Table 1). In multivariable logistic regression adjusted for age group and HIV status, participants with at least one CH mutation were more likely to be frail than those without any CH mutation (adjusted odds ratio [aOR] 2.38, 95% CI 1.01, 5.67, p = 0.049). HIV infection was not associated with frailty on multivariable regression adjusting for any CH mutation and age group (aOR 1.06, 95% CI 0.45, 2.47, p = 0.88) (Figure 2A and Table S3, "Multivariable model I"). Of note, in a multivariable model adjusted for HIV infection, age group, gender, sexual orientation, body mass index (BMI), and smoking, the model estimates for CH mutation and frailty association were similar and no other factors were significantly associated with frailty (Table S3, "Multivariable model II"). In an additional multivariable model adjusted for CH mutation, age group HIV infection, and inflammatory biomarkers (high-sensitive C-reactive protein [hs-CRP] and interleukin-6 [IL-6]), the estimates for the association between CH and frailty were similar and inflammatory biomarkers were not significantly associated with frailty (Table S3, "Multivariable model III").

Multimorbidity

Multimorbidity was present in 162 (47%) participants (Table 1). In multivariable logistic regression adjusted for age, gender, sexual orientation, HIV status, BMI, smoking, and baseline inflammatory markers (hs-CRP and IL-6), CH was not significantly associated with multimorbidity (aOR 1.46, 95% CI 0.84, 2.53, p = 0.18) but not surprisingly, older age (>65 vs. ≤65 years) and higher BMI (≥25 vs. <25 kg/m^2) were associated (Figure 2B, and Table S4).

Phenotypic age acceleration

Of all participants included, the median phenotypic age was 68.3 (IQR 62.7, 74.6) years, compared with the median chronologic age of 67 (IQR 62–72); the median phenotypic age acceleration (PAA) was 0.6 (IQR −2.5, 5.0) years (Table 1). In multivariable linear regression adjusted for presence of any CH mutation, gender, sexual orientation, BMI, and smoking, participants with HIV infection had higher PAA than those without HIV (adjusted coefficient 1.73, 95% CI 0.30, 3.16, p = 0.018) (Figure 2C and Table S5).

Quality of life

Overall, the median quality of life (QoL) score (n = 280) was 36 (IQR 29, 39) (Table 1). In multivariable linear regression, participants with at least one CH mutation were more likely to have reduced QoL compared with those without any CH mutation (adjusted coefficient −2.18, 95% CI −3.92, −0.44, p = 0.014) after adjusting for age, HIV status, gender, sexual orientation, BMI, smoking, frailty, activities of daily living (ADL) dependency, and instrumental activities of daily living (IADL) dependency. HIV infection was not associated with reduced QoL (adjusted coefficient −0.65, 95% CI −2.12, 0.81, p = 0.38). Smoking, ADL dependency, and IADL dependency were also independently associated with reduced QoL (Figure 2D and Table S6).

CH-specific factors and geriatric outcomes

Having a CH mutation with a variant allele fraction (VAF) ≥5% (if multiple CH mutations were recorded, the highest VAF of all mutations was used) was present in 38 (11%) of all 345 participants and 38 (48%) of the 79 participants with any CH mutation. Sixteen (4.7%) of all 345 participants had any CH mutation with a VAF ≥10% (Table 1). In adjusted analyses, having any CH mutation with a VAF ≥5%, compared to having CH mutations with VAF <5% or having no CH mutations, was not associated with an increased odds of frailty, multimorbidity, or increased PAA (Tables S7 and S8), but was associated with reduced QoL, after adjusting for age, gender, sexual orientation, HIV status, BMI, smoking, frailty, ADL dependency, and IADL dependency (Table S8).

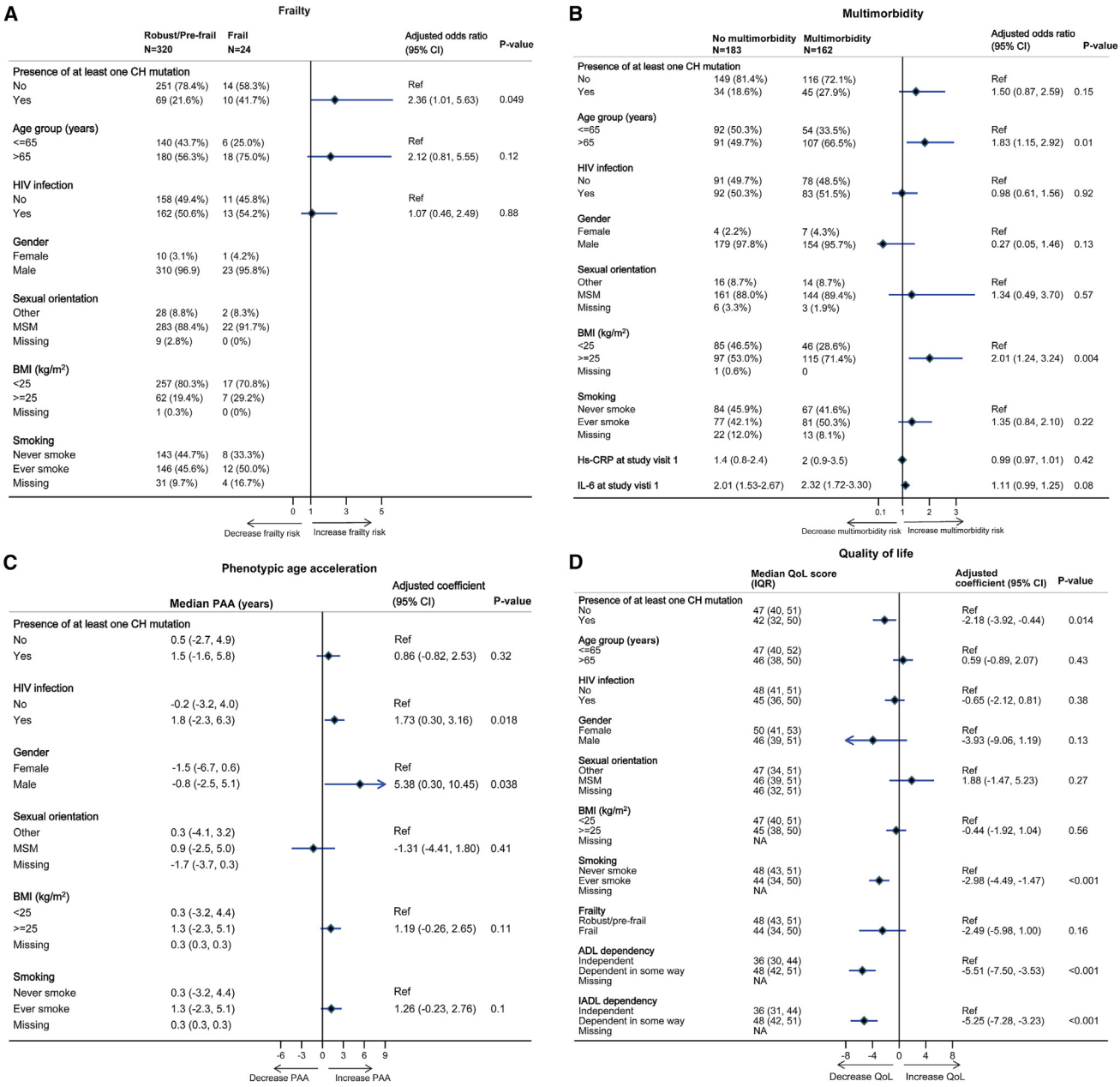

Figure 2. Associations between clonal hematopoiesis, HIV infection, and primary geriatric outcomes

The reference line (Ref) represents an odds ratio of 1 (no effect) or a coefficient of 0 (no effect). Data are presented as odds ratios and 95% confidence intervals (CI) or coefficients and 95% CI. Logistic regression was used to calculate the adjusted odds ratio for the outcomes: frailty (A) and multimorbidity (B). Linear regression was used to calculate the adjusted coefficients for PAA (C) and QoL (D).

(A) For frailty, we adjusted for the presence of any CH mutation, age group, and HIV status.

(B) For multimorbidity, we adjusted for the presence of any CH mutation, age group, gender, HIV status, BMI, smoking status, sexual orientation, and inflammatory markers (hs-CRP and IL-6).

(C) For PAA, we adjusted for the presence of any CH mutation, HIV status, gender, sexual orientation, BMI, and smoking status.

(D) For QoL, we adjusted for the presence of any CH mutation, age group, HIV status, gender, sexual orientation, BMI, smoking status, frailty, and ADL and IADL dependency. Abbreviations: CH, clonal hematopoiesis; PAA, phenotypic age acceleration; QoL, quality of life; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; ADL, activities of daily living; IADL, instrumental activities of daily living.

We also investigated whether participants with *DNMT3A*, *ASXL1*, and *TET2*, the three most commonly mutated CH genes in this cohort[22] (Table S9), were at higher risk for geriatric outcomes. In multivariable analyses, participants with *DNMT3A*, *ASXL1*, and *TET2* genes were associated with an increased risk of frailty and reduced QoL although the statistical

Table 2. HIV-related factors associated with multimorbidity, frailty, PAA, and QoL in study participants with HIV

	Multimorbidity						*Frailty* (vs. *pre-frail/robust*) [b]			*PAA*[b]			*QoL*[b]		
	Univariable			Multivariable[a]			Univariable			Univariable			Univariable		
HIV-related parameters	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	Coef	95% CI	*p* value	Coef	95% CI	*p* value
Current CD4, cells/mm^3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
<500	Ref.	–	–	–	–	–	Ref.	–	–	Ref.	–	–	Ref.	–	–
≥ 500	1.31	0.67	2.57	0.43	–	–	0.81	0.24	0.28	0.74	0.52	−1.80	2.85	0.66	−0.07	−2.9	2.76	0.96
Nadir, cells/mm^3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
<200	Ref.	–	–	–	–	–	Ref.	–	–	Ref.	–	–	–	–	Ref.	–	–	–
≥ 200	0.87	0.47	1.61	0.65	–	–	1.27	0.37	4.29	0.70	−0.82	−2.95	1.32	0.45	0.88	−1.71	3.48	0.50
Duration of HIV (per year increase)	1.03	0.99	1.06	0.15	–	–	1.01	0.94	1.08	0.78	−0.20	−0.14	0.10	0.74	−0.02	−0.16	0.12	0.79
Duration of ART (per year increase)	1.05	1.01	1.11	0.032	1.06	1.01	1.12	0.021	1.04	0.95	1.13	0.40	−0.03	−0.17	0.11	0.64	0.1	−0.07	0.27	0.24

Univariable analysis for multimorbidity (yes vs. no) and frailty (vs. pre-frail/robust) outcomes were modeled using logistic regression. PAA and QoL outcomes were modeled using linear regression.

Abbreviations: PAA, phenotypic age acceleration; QoL, quality of life; ART, antiretroviral therapy; OR, odds ratio; Coef, coefficient.

[a]Multivariable model was adjusted for age, gender, sexual orientation, BMI, and smoking.

[b]Multivariable models for frailty, PAA, and QoL were not conducted due to insignificant associations of HIV-related parameters in the univariable analysis.

significance for the association with frailty was borderline (OR, 2.37, 95% CI 0.98, 5.74, p = 0.056). The association with reduced QoL, however, reached statistical significance with a p value of 0.012 (coefficient −2.36, 95% CI −4.19, −0.53) (Table S10). We did not find the association of these genes with other geriatric outcomes such as multimorbidity or PAA, but participants with *ASXL1* gene exhibited a potential increased risk for multimorbidity (3.64, 95% CI 0.95, 15.57, p = 0.06), even adjusted for smoking history, suggesting a trend toward significance (though low numbers limited interpretation).

HIV-specific factors and geriatric outcomes

We further investigated whether there were associations between HIV-specific factors such as current CD4 count, nadir CD4 count, duration of HIV and duration of ART, and geriatric outcomes (frailty, multimorbidity, QoL, and PAA) (Table 2). Most HIV-specific factors were not associated with frailty, multimorbidity, and PAA outcomes after adjusting for confounders, except for the time the participant had been taking ART, which was found to be associated with multimorbidity (per year increase: aOR 1.06, 95% CI 1.01, 1.12, p = 0.021) after adjusting for age, gender, sexual orientation, BMI, smoking, and current CD4 count.

Sensitivity analyses

We conducted a sensitivity analysis excluding individuals with HBV or HCV co-infection. The results did not change meaningfully from the primary analyses, except that the association between CH mutation and frailty became slightly weaker, likely due to smaller sample size (Table S12). Moreover, we additionally adjusted both hs-CRP and IL-6 for frailty outcomes (Table S3, "Multivariable model III") and QoL (Table S6, "Multivariable model II") as sensitivity analyses, and the results are consistent with the primary analyses.

DISCUSSION

In the ARCHIVE cohort of adults aged >55 years old with and without HIV, participants with CH at enrollment into the cohort had an increased risk of frailty and reduced QoL measured at the second study visit, suggesting that aging-related molecular processes such as CH may correlate with an increased risk of these adverse aging-related outcomes. While participants with HIV did not have increased frailty or reduced QoL compared to participants without HIV, which is likely reflective of the overall robustness of our study population, having HIV was associated with PAA, a measure of aging that has been predictive of mortality in the general population,[31] but not previously been demonstrated in people with HIV.[32]

Frailty is a dynamic and complex age-related syndrome that represents a state of vulnerability to adverse health outcomes occurring in response to a wide variety of stressors.[33] Though an association between CH and frailty has not been previously published, measures of frailty, such as the FRAIL score used in this study, often account for comorbidities that CH is known to be associated with, such as malignancies,[34–36] heart disease, lung disease,[37] and stroke.[28] In our cohort, we did find that there was a higher proportion of participants with CH that had

comorbidities than people without CH, though this needs to be validated in larger cohorts to evaluate the role that the presence of these comorbidities plays in the association between CH and frailty in people with HIV. In addition, the emergence and growth of CH clones are supported by inflammatory environments,[29] which are also associated with frailty,[3] and CH is linked to a wide range of comorbidities that are also driven by inflammation[28–30] and also associated with frailty.[38–40] Despite these correlations between CH, comorbidities, inflammation, and frailty, the independent association between CH and frailty after adjustment of other risk factors for comorbidities (such as age, gender, smoking, BMI, IL-6, and hs-CRP) suggests that the association between CH and frailty stands independent of these other related covariates.

Similar to frailty, reduced QoL was also associated with CH in our cohort. The CASP-19 QoL scale (Table S11) is made up of four domains, two of which are control and autonomy, which refer to the things that an individual would like to do and may reflect some measure of physical function. While it is possible that the increased risk of comorbidities associated with CH may directly impact physical function and therefore control and autonomy, thereby reducing QoL,[41] the independent association between CH and QoL persisted in our multivariable models adjusting for risk factors for comorbidity development, such as age, gender, smoking, BMI, frailty, ADL dependency, and IADL dependency. The other two domains of the CASP-19 are pleasure and self-realization, which include aspects of enjoyment, happiness, satisfaction, and optimism about the future. While not substantively explored to date, CH may be associated with neurocognitive conditions[42] that may impact these QoL domains. Importantly, QoL did not differ across HIV status in our population.

Our findings that HIV infection is associated with PAA are consistent with previous literature demonstrating that molecular or biological aging is accelerated in people with HIV.[43–45] In addition, phenotypic age is associated with comorbidities[31] and is made up of biochemical and hematological measures, as well as C-reactive protein, which are elevated in people with HIV compared to people without HIV. While a cross-sectional study in Thailand among 333 people with HIV and 102 people without HIV did not identify that PAA was associated with HIV,[32] the median age in that study was younger than ours (55 vs. 67), which may account for this difference. Interestingly, while CH was not associated with PAA in total cohort, among those without HIV, there was a trend toward an increased PAA among participants with CH, though the association did not meet statistical significance. Given that CRP is a component of phenotypic age and has been shown to be elevated in people with CH,[22,31] and that PAA is associated with an increased risk of morbidity and mortality in the general population,[31] these results warrant further validation in larger cohorts of people without HIV.

Limitations of the study

The results of our study have several considerations. First, our frailty assessment relied upon participant self-report rather than a more comprehensive evaluation including measures of strength and physical function such as hand grip and walking speed. Second, a significant proportion of participants were LTFU from the first to second study visit, which may not be surprising given the age of our study population and the timing of the study visit relative to the COVID-19 pandemic. More LTFU participants were enrolled from tertiary care centers, suggesting that these participants may have been more medically complex (i.e., sicker), or that due to tertiary care outpatient clinic closures during COVID-19 pandemic lockdowns, participants from these enrolling sites may have transferred their care to primary care centers. Third, we compared our geriatric outcomes measured at study visit 2 with CH testing results obtained from the first study visit; however, published longitudinal data on CH do not suggest that the prevalence of CH increases significantly over three to four years.[46] CH testing results from study visit 2 are forthcoming. Lastly, we did not obtain data on geriatric outcomes at study visit 1, so we were unable to correlate longitudinal changes in these outcomes over the time period between the two study visits with HIV and CH.

In conclusion, our results suggest that CH is associated with frailty and reduced QoL and that HIV is associated with PAA. While further evaluation and validation of the association between CH and frailty and QoL is warranted, data from our study suggest that CH may be used as a biomarker for these aging-related outcomes. Such screening may be used to prioritize high-risk individuals for interventions such as exercise programs or pharmacologic interventions that address metabolic and inflammatory conditions associated with frailty.[47,48] Further exploration of the pathophysiology behind the links between CH and geriatric outcomes may validate our findings in other populations and help to design targeted strategies to reduce these outcomes and add quality to life years.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Win Min Han (wmhan@kirby.unsw.edu.au).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The data that support the findings of this study are available from the lead author upon request. This paper does not report the original code. Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon request.

CONSORTIA

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AUTHOR CONTRIBUTIONS

M.N.P., K.P., P.Y., and N.J.D. conceived and designed the study. P.Y. and N.J.D. designed the statistical analysis plan and W.M.H. performed the statistical analysis. E.B.-R. contributed to study conduct and ascertainment of data and resolution of data queries. W.M.H. and H.M.S.S. wrote the first draft of the manuscript and revised the subsequent drafts. W.M.H., H.M.S.S., M.N.P., K.P., P.Y., and N.J.D. reviewed all manuscript versions and interpreted the data. W.M.H. and N.J.D. accessed and verified the data. All authors contributed data to the study and to the interpretation of the results and revised the manuscript. All authors were permitted to access the primary data and final analyzed datasets. All authors approved the final version of the manuscript to submit for publication.

DECLARATION OF INTERESTS

M.B. has received funding from Gilead Sciences and ViiV Healthcare for lecturing and traveling to scientific meetings and medical advisory boards. D.A.B. has received funding and travel grants from and served on advisory boards for ViiV Healthcare and Gilead. D.E.S. has received consultancy fees and lecturing honorarium from ViiV Healthcare and Gilead Sciences. J.F.H.'s institution has received reimbursement for her participation in advisory boards for Gilead Sciences and ViiV Healthcare. I.W.'s institution has received financial or in-kind support for his role in clinical studies from Moderna, CSL, MSD, Gilead, and ViiV. G.V.M. has received research funding from Gilead, AbbVie, Janssen, and ViiV, has served on advisory boards for AstraZeneca and ViiV, and has provided consultancy and received travel support from Gilead.

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STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Whole blood DNA (ARCHIVE cohort)	Dharan et al.[22]	N/A
Critical commercial assays		
48.48 Access Array™ Loading Reagent Kit	Fluidigm	100–1032
MiSeq Reagent Kit v3	Illumina	MS-102-3001
Oligonucleotides		
Targeted sequencing (TS) primers	Dharan et al., Yeh et al.[22,49]	N/A
ASXL1 c.1934dupG primers	Yannakou et al.[50]	N/A
Software and algorithms		
PathOS (Targeted Sequencing analysis)	Doig et al.[51]	N/A
GeneMarker Software	Yannakou et al.[50]	N/A
Other		
Variant sequencing results and analysis	Dharan et al.[22]	N/A

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Clinical cohort

The ARCHIVE cohort and study procedures for the first study visit have been published previously.[22] In brief, the first visit of the study enrolled participants over the age of 55 years from six primary-care centers and three tertiary hospitals in Sydney and Melbourne, Australia from 20 December 2017 to 29 November 2018. In total, 446 adults >55 years of age were enrolled: 220 with HIV and 226 without HIV. Participants without HIV were required to have a negative HIV test within 12 months of enrollment. The main objectives of the first study visit were to compare the prevalence of CH across HIV status and to describe the relationship between HIV, CH, and inflammatory biomarkers.

Here we report the results from the second study visit, which was conducted from 15 March 2021 to 5 October 2022. The second study visit included review of the participant's medical record, an assessment of frailty, and collection of a blood sample. Demographic and clinical data that were retrieved from participants' medical records included age, HIV status, date of last negative HIV test for participants without HIV, and HIV-related data for participants with HIV including the most recent CD4 count and HIV viral load, and current ART regimen. Frailty was assessed by the site study coordinator as described below. All participants were asked to complete a questionnaire on their education, household income, employment status, use of tobacco, alcohol, recreational drugs, the number of medications they take, as well as an assessment of QoL, ADL[52] and IADL.[53] The questionnaire was completed either online at the participants' home or in the clinic, or on paper at the clinic.

Data on gender and sexual orientation were obtained from the first study visit by asking the enrolling clinical site to report the participant's gender and whether the participant was sexually active with men, women, or both. Men who have sex with men (MSM) were defined as male participants who were reported by the clinical site as having sex with either men only or both men and women. CH testing results including the VAF (the proportion of all gene copies that contain the mutation) were obtained from the results of testing a blood sample obtained at the enrollment visit (2017–2018).

Ethics statements

The research protocol, consent form and associated documents were approved by the St Vincent's Hospital Human Research Ethics Committee in New South Wales, Australia. All individuals gave written informed consent to participate in the study. The study was registered with ClinicalTrials.gov (NCT04641013).

METHOD DETAILS

Whole-blood sample processing

Participants' whole blood was collected in EDTA tubes and DNA was extracted using the QIAsymphony DNA Midi Kit (Qiagen, 931255) using the manufacturer's protocols.

Targeted deep sequencing

Participant screening for clonal hematopoiesis (CH) was conducted using whole-blood DNA as previously described. To restate the methodology, A targeted sequencing (TS) amplicon panel targeting 55 genes commonly mutated in hematologic malignancies was utilized (Table S9). The testing was performed without knowledge of the participants' HIV status to prevent bias. The Fluidigm Access Array system was used for target-specific amplification, followed by tagging, pooling, and purifying the amplified products. Sequencing was carried out on Illumina MiSeq or NextSeq platforms with 150-bp reads, and results were mapped to the human reference genome (hg19) using BWA-MEM. Variants were identified through an in-house pipeline,[51] with only those showing significant coverage and a variant allele fraction over 1% being considered for further analysis. Artifacts and common variants were excluded, and the remaining variants were annotated for their relevance.[54]

For the *ASXL1* c.1934dupG variant, fragment-length analysis was performed alongside TS to avoid false positives due to PCR artifacts. PCR amplification targeting the ASXL1 gene was conducted using primers specific to the region of interest.[50] The amplified DNA fragments were then denatured and analyzed using capillary electrophoresis on the Applied Biosystems 3730 Genetic Analyzer.[50] The resulting data were processed and interpreted with the GeneMarker software. Positive results from fragment-length analysis were confirmed if the variant was detected in TS with more than 5% variant allele fraction (VAF).

Geriatric outcomes

Frailty

Frailty was defined using the FRAIL score,[33,55] an assessment of frailty that has not previously been used in people with HIV but is recommended for frailty screening in people with HIV in international guidelines.[56] The FRAIL score includes the following components: 1) unintentional weight loss >5% within the past 12 months, 2) fatigue, 3) difficulty walking on flat surfaces, 4) difficulty walking upstairs, and 5) >5 illnesses out of 11: diabetes, hypertension, lung disease, cancer, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, kidney disease. All components of the FRAIL score are based on participant self-report; unintentional weight loss >5% was calculated based on participant self-reporting of their current weight and weight one year prior. Participants were categorized using the FRAIL score as: frail, pre-frail and robust.

Phenotypic age and phenotypic age acceleration

Phenotypic age was calculated using nine biochemical and blood count characteristics: albumin, creatinine, glucose, hs-CRP, lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, white blood cell count.[31] PAA was defined as the difference between phenotypic age and chronological age, denoting phenotypic age adjusted for chronological age. Therefore, PAA quantifies the extent to which an individual's physiological age differs from their chronological age, indicating accelerated aging for a positive value. PAA has been shown to be highly predictive of all-cause mortality in a large diverse cohort study among the general population.[31]

Multimorbidity

Multimorbidity was defined as having two or more comorbidities (of the 11 collected by participant report in the FRAIL questionnaire above).

Quality of life (QoL)

QoL was defined using the CASP-19, a 19-point scale using four domains: control, autonomy, pleasure and self-realization to measure the QoL in older age.[57] The nineteen items include: six for control, five for autonomy, four for pleasure and four for self-realization. Response options are on a 4-point Likert scale ranging from 0 (never) to 3 (often).

QUANTIFICATION AND STATISTICAL ANALYSIS

Descriptive statistics were used to compare characteristics across participants living with HIV and participants without HIV. P-values for comparisons were generated using the chi-square test. The aim of this analysis was to determine whether HIV infection or the presence of CH mutations were associated with the primary outcomes of interest: frailty, PAA, multimorbidity and QoL. We analyzed frailty as a categorical outcome (frail vs. pre-frail/robust), PAA as a continuous outcome (1 year increase in PAA), multimorbidity as a categorical outcome (present vs. absent) and QoL as a continuous outcome (one point increase in QoL scale).

We used multivariable logistic or linear regression to investigate the factors associated with the geriatric outcomes, as appropriate. Multivariable models included demographic and/or clinical characteristics including age group ($\leq$65/>65 years), gender, sexual orientation, HIV status, CH mutation, whether the participant had ever smoked, BMI (<25/$\geq$25 kg/m^2), baseline inflammatory markers (hs-CRP and IL-6), ADL dependency[58] and IADL dependency.[59] Variables were included in the multivariable models if they were either significantly associated with the outcome on univariate analysis (p-value <0.1) or known confounders or covariates of interest (included *a priori*), as appropriate for the specific model for each outcome. Of note, due to the low number of frailty outcomes (n = 24), we only adjusted for any CH mutation, age group and HIV status in the multivariable frailty model to avoid overfitting the model.

We also explored whether specific characteristics of CH mutations were associated with the geriatric outcomes including having a CH mutation with a VAF $\geq$5% (larger clonal population size) vs. having a CH mutation with VAF<5% or having no CH mutations; and having mutations in the most commonly mutated genes (DNMT3A, ASXL1 or TET2) vs. having a CH mutation in other genes or having no CH mutations. If an individual had multiple mutations, the analysis was done using the highest VAF, defined as the single highest

VAF value among all CH mutations. We conducted a sensitivity analysis excluding participants with HBV or HCV co-infection and adjusted for baseline inflammatory markers (IL-6 and hs-CRP) for frailty and QoL and in addition to the confounders mentioned above. The data analysis was conducted using Stata 17.0 (StataCorp, College Station, TX).

Additional resources

The study was part of the trial and is registered with ClinicalTrials.gov (NCT04641013).