Long-term evolution of comorbidities and their disease burden in individuals with and without HIV as they age: analysis of the prospective AGE$_h$IV cohort study

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Summary

Background People with HIV generally have more ageing-associated comorbidities than those without HIV. We aimed to establish whether the difference in comorbidities and their disease burden changes with ageing.

Methods In this prospective, longitudinal cohort study, we assessed comorbidities commonly associated with ageing every 2 years in 596 HIV-positive and 550 HIV-negative participants. HIV-positive participants were recruited from the HIV outpatient clinic of the Amsterdam University Medical Centres (Amsterdam, Netherlands). HIV-negative participants were recruited from the sexual health clinic and the Amsterdam Cohort Studies at the Public Health Service of Amsterdam (Amsterdam, Netherlands). Inclusion criteria were participants aged 45 years or older and, for HIV-negative participants, a documented HIV-negative antibody test. The mean number of comorbidities present over time was compared between groups by use of Poisson regression, accounting for dropout and death through joint survival models. Mean disability-adjusted life-years (DALYs) accrued during 2-year intervals were compared between groups by use of an exponential hurdle model.

Findings Between Oct 29, 2010, and Oct 9, 2012, participants were enrolled and then prospectively followed up until their last visit before Oct 1, 2018. 1146 participants were followed up for a median 5·9 years (IQR 5·7–6·0), during which 231 participants (20·2%) dropped out: 145 (24·3%) of 596 HIV-positive and 86 (15·6%) of 550 HIV-negative. 38 (3·3%) of 1146 participants died: 31 (5·2%) of 596 HIV-positive and seven (1·3%) of 550 HIV-negative. 24 HIV-positive and two HIV-negative participants died from ageing-associated comorbidities. 15 HIV-positive participants versus one HIV-negative participant died from non-AIDS malignancies. At inclusion, mean number of comorbidities was higher in HIV-positive participants (0·65) than in HIV-negative participants (0·32; p<0·0001). Mean number of comorbidities increased at similar rates over time: rate ratio (RR) per year for HIV-positive participants 1·04 (95% CI 1·00–1·08), RR per year for HIV-negative participants 1·05 (1·01–1·08; $p_{interaction}$=0·78). Number of comorbidities was associated with an increased risk of death (hazard ratio 3·33 per additional comorbidity, 95% CI 2·27–4·88; p<0·0001). HIV-positive participants had higher increases in mean DALYs than HIV-negative participants (0·209 per year, 95% CI 0·162–0·256 *vs* 0·091 per year, 0·025–0·157; $p_{interaction}$=0·0045). This difference was reduced when deaths were excluded in establishing DALYs (0·127, 0·083–0·171 *vs* 0·066, 0·005–0·127; $p_{interaction}$ =0·11).

Interpretation The larger comorbidity prevalence in HIV-positive participants aged 50–55 years on effective antiretroviral treatment than in HIV-negative participants increased similarly as participants aged and was associated with an increased risk of death, particularly of non-AIDS malignancies. Our findings reinforce the need for strategies to optimise prevention, screening, and early intervention.

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Introduction

Wherever effective antiretroviral treatment is universally implemented, AIDS as a cause of death has substantially diminished, HIV has become a manageable chronic condition,[1,2] and life expectancy of people with HIV on long-term antiretroviral treatment has approached that of the general population.[3] Consequently, ageing-associated comorbidities increasingly account for morbidity and mortality among people with HIV.[4–8] Despite viral suppression, people with HIV are disproportionately affected by comorbidities compared with the general population.[4–6] Whether the comorbidity prevalence in people with HIV taking effective antiretroviral treatment remains constant or increases with continued ageing remains unclear.

We should consider both comorbidity prevalence and its associated disease burden as comorbidities differ in their effect on health. For example, malignancies influence wellbeing of individuals more profoundly than

Research in context

Evidence before this study

On Nov 1, 2021, we searched PubMed for articles and conference abstracts in English from the Conference on Retroviruses and Opportunistic Infections and European AIDS Conference using the free-text or MeSH terms "HIV", "HIV infection", "comorbidities", "age-related/associated disease", "kidney/renal", "diabetes mellitus type II", "cardiovascular disease", "malignancies/cancer", or "osteoporosis" in titles, abstracts, and keywords. Our search provided 677 studies, of which nine were longitudinal. Of those nine, three included HIV-negative control groups (two of which were prospective) but focused solely on kidney disease or type 2 diabetes.

Added value of this study

To our knowledge, we are the first to assess the longitudinal evolution of a broad range of comorbidities in people with HIV aged between 45 and 65 years on antiretroviral treatment compared with HIV-negative control individuals with similar demographic characteristics. We found that the mean number of comorbidities remained higher in HIV-positive participants than in HIV-negative participants, but without evidence of further diversion over time. A higher number of comorbidities was associated with higher mortality, which was particularly observed among people with HIV, most notably from non-AIDS malignancies. Furthermore, we examined the disease burden from comorbidity over time using disability-adjusted life-years (DALYs). The DALY measure enables an analysis of morbidity while considering the severity of the disease and mortality. Although HIV-positive participants incurred more DALYs than HIV-negative participants, this difference disappeared when deaths were excluded from this statistic. After the exclusion of deaths, the difference in DALYs was largely driven by the higher mortality of HIV-positive participants from ageing-associated comorbidities.

Implications of all the available evidence

Comorbidity prevalence in people with HIV on effective antiretroviral treatment increases with age at a similar rate to that in people without HIV; however, comorbidities remain more prevalent and are associated with more years of life lost, particularly because of malignancy-related deaths. Prevention, screening, and early intervention for ageing-associated comorbidities and non-AIDS malignancies in particular need to be optimised for people with HIV.

osteoporosis or diabetes. One meaningful way to evaluate disease burden is to estimate disability-adjusted life-years (DALYs).[7] DALYs reflect the disease burden in a population by combining morbidity severity and mortality.

See Online for appendix 2

We aimed to compare both evolution of ageing-associated comorbidity prevalence (particularly physical comorbidities) and associated disease burden over a time period of up to 6 years between HIV-positive and HIV-negative participants in a prospective cohort.

Methods

Study population and design

AGE$_h$IV is an ongoing prospective cohort study examining the occurrence of ageing-associated comorbidities in HIV-positive and HIV-negative participants. HIV-positive participants were recruited from the HIV outpatient clinic of the Amsterdam University Medical Centers (Amsterdam, Netherlands). HIV-negative participants were recruited from the sexual health clinic and the Amsterdam Cohort Studies at the Amsterdam Public Health Service (Amsterdam, Netherlands).[8] Recruiting the control group of HIV-negative participants from a sexual health clinic allowed for a comparable group regarding sexual orientation, geographical region, and sociodemographic background. Inclusion criteria were being aged 45 years or older and, for controls, a documented HIV-negative antibody test at enrolment. Between Oct 29, 2010, and Oct 9, 2012, 1148 participants were enrolled. This study has been registered at ClinicalTrials.gov (NCT01466582).

Once every 2 years, participants had a standardised assessment for the presence of age-related comorbidities (appendix 2 p 2). HIV-negative participants were tested for HIV with a fourth-generation test at each study visit. Detailed data about past and current HIV-related and treatment-related characteristics were obtained from the Dutch HIV Monitoring Foundation.[9] Cancer screening was done according to guidelines for the Dutch general population and guidelines of the Dutch Association of HIV Treating Physicians (appendix 2 p 2). Written informed consent was obtained from all participants and the study was approved by the ethics committee of the Amsterdam University Medical Centers.

For the current analysis, we used data from both the enrolment visit and three follow-up study visits, which were prospectively collected until Oct 1, 2018. All participants who had at least one study visit were included in the analysis (596 HIV-positive participants and 550 HIV-negative participants).

Outcomes

Comorbidities considered were non-AIDS malignancies, congestive heart failure, cardiovascular and cerebrovascular disease (eg, myocardial infarction, angina pectoris, peripheral arterial disease, and cerebrovascular events [ie, ischaemic and haemorrhagic strokes, but not transient ischaemic attacks]), chronic obstructive pulmonary disease (COPD), type 2 diabetes, kidney disease, and osteoporosis (appendix 2 p 3). Confirmed comorbidities were established on the basis of assessments during study visits for COPD, diabetes,

kidney disease, and osteoporosis and on the basis of medical records for non-AIDS malignancies, congestive heart failure, and cerebrovascular disease.[6] Obesity, hypertension, and dyslipidaemia were considered risk factors for comorbidities rather than as comorbidities.

Self-reported diagnoses were validated with medical records from the Amsterdam University Medical Centers for HIV-positive participants and with medical records from a general practitioner for HIV-negative participants, provided consent to contact the general practitioner was obtained. Unvalidated diagnoses were used when validation was not possible (eg, participants not providing consent or absence of clinical documentation). To estimate the comorbidity count, we counted the total number of comorbidities present in a person during the 24 months before each study visit (ie, period prevalence).

We recorded the date of onset and resolution for each comorbidity and evaluated whether each comorbidity was present or absent at each study visit. We adapted additional considerations for the presence of specific comorbidities. We considered peripheral arterial disease, congestive heart failure (including if preceded by a myocardial infarction), and ischaemic and haemorrhagic strokes to be present during all study visits after initial diagnosis. We considered malignancies to be present for 5 years after initial diagnosis. If participants developed a different malignancy, we counted the second malignancy as a separate comorbidity. We did not consider myocardial infarction to remain present after its initial diagnosis (appendix 2 p 12).

Date and cause of death were provided by the treating HIV doctor or the study doctor in collaboration with the general practitioner by use of the Coding Causes of Death form.[10] If participants were lost to follow-up or withdrew consent, vital status (ie, whether an individual is alive or dead) and causes of death were obtained through the Municipal Personal Records Database.[11]

We estimated DALYs for each participant during the 24 months before each study visit using a pure prevalence approach.[12] DALYs were calculated as the sum of years lost to disability and years of life lost to premature death (appendix 2 pp 3–4). To account for multiple comorbidities occurring during overlapping time periods, a combined disability weight was calculated with the multiplicative approach.[13]

Statistical analysis

We examined the longitudinal changes in comorbidity count over time while accounting for mortality and dropout simultaneously using joint models.[14] The mean total number of comorbidities occurring within the 24 months before each study visit (ie, period prevalence) was estimated at each study visit as a submodel of two joint survival models by use of Poisson regression with adjustment for age at inclusion. We added a random intercept to account for variability between participants at baseline. We included HIV status and the interaction

	HIV positive (n=596)	HIV negative (n=550)	p value
Demographics			
Age, years	52 (48–59)	52 (48–58)	0·33*
Male sex at birth	522/596 (87·6%)	465/550 (84·6%)	0·14†
Female sex at birth	74/596 (12·4%)	85/550 (15·4%)	..
Sexual behaviour in men	..	..	0·081†
MSM‡	407/522 (78·0%)	369/465 (79·4%)	..
Non-MSM	84/522 (16·1%)	82/465 (17·6%)	..
Missing	31/522 (5·9%)	14/465 (3·0%)	..
Ethnicity	..	..	<0·0001†
Other than White	74 (12·4%)	23 (4·2%)	..
White	522 (87·6%)	526 (95·6%)	..
Missing	0	1 (0·2%)	..
Higher education§	220 (36·9%)	289 (52·6%)	<0·0001†
Missing	63 (10·6%)	32 (5·8%)	..
Behavioural characteristics			
Smoking status	..	..	0·0008†
Never smoked	178 (29·9%)	193 (35·1%)	..
Former smoker	191 (32·1%)	204 (37·1%)	..
Current smoker	174 (29·2%)	129 (23·5%)	..
Missing	53 (8·9%)	24 (4·4%)	..
Pack years if ever smoked	21·8 (7·8–36·0)	15·0 (4·5–28·8)	0·0001*
Alcohol use	..	..	<0·0001†
Never	51 (8·7%)	36 (6·6%)	..
Former drinker	82 (13·8%)	35 (6·4%)	..
Current drinker	431 (72·3%)	462 (84·0%)	..
Missing	32 (5·4%)	17 (3·1%)	..
Heavy daily alcohol use in the past 6 months¶	18 (3·0%)	34 (6·2%)	0·0002†
Missing	63 (10·6%)	28 (5·1%)	..
Binge alcohol drinking during the past 6 months‖	110 (18·5%)	164 (29·8%)	<0·0001†
Missing	83 (13·9%)	36 (6·6%)	..
Any injection drug use	19 (3·2%)	6 (1·1%)	<0·0001†
Missing	65 (10·9%)	27 (4·9%)	..
Tetrahydrocannabinol use in the 6 months preceding study enrolment	72 (12·1%)	57 (10·4%)	0·0006†
Missing	64 (10·7%)	27 (4·9%)	..
Body composition			
Waist circumference, cm	93·4 (86·4–100·2)	90·7 (84·8–97·7)	0·0016**
Hip circumference, cm	96·6 (92·1–100·9)	99·1 (95·6–103·3)	0·0001**
Waist to hip ratio	0·97 (0·92–1·01)	0·92 (0·87–0·96)	0·0001**
BMI, kg/m²	24·3 (22·4–26·7)	24·5 (22·9–27·1)	0·021**
Comorbidity††			
Number of ageing-associated comorbidities	..	..	<0·0001†
0	331 (55·5%)	408 (74·2%)	..
1	175 (29·4%)	118 (21·5%)	..
2	65 (10·9%)	17 (3·1%)	..
≥3	25 (4·2%)	7 (1·3%)	..
Hypertension grade 2‡‡	156 (26·2%)	92 (16·7%)	0·0003†
Missing	0 (0%)	1 (0·2%)	..
Hepatitis B surface-antigen-positive	38 (6·4%)	3 (0·6%)	<0·0001†
Missing	0 (0%)	3 (0·6%)	..
Hepatitis C virus RNA-positive	21 (3·5%)	6 (1·1%)	0·0001†
Missing	0 (0·0%)	3 (0·6%)	..

(Table 1 continues on next page)

	HIV positive (n=596)	HIV negative (n=550)	p value
(Continued from previous page)			
Cytomegalovirus IgG-positive	563 (94·5%)	414 (75·3%)	<0·0001†
Missing	0 (0·0%)	2 (0·4%)	..
Depressive symptoms	..	..	<0·0001†
CES-D ≤8	278 (46·6%)	345 (62·7%)	..
CES-D 8–16	128 (21·5%)	94 (17·1%)	..
CES-D ≥16	129 (21·6%)	85 (15·5%)	..
Missing	61 (10·2%)	26 (4·7%)	..
Fried frailty phenotype§§	..	..	<0·0001†
Robust	214 (35·9%)	333 (60·6%)	..
Prefrail	312 (52·3%)	200 (36·4%)	..
Frail	68 (11·4%)	17 (3·1%)	..
Missing	2 (0·3%)	0 (0%)	..
Self-reported cancer screening history			
Breast in women	48 (64·9%)	71 (83·5%)	0·0068
Cervix in women	50 (67·6%)	77 (90·6%)	0·0003
Anal in men	206 (39·5%)	1 (0·2%)	<0·0001
Colon	86 (14·4%)	94 (17·1%)	0·22
Markers of inflammation			
hsCRP, mg/L	1·5 (0·7–3·5)	1·0 (0·6–2·0)	0·0001*
D-dimer, mg/L	0·22 (0·20–0·35)	0·25 (0·20–0·39)	0·011*
IL-6, pg/mL	1·5 (1·0–2·9)	1·9 (1·2–3·2)	0·0001*
sCD14, ng/mL	1587 (1305–2009)	1357 (1081–1745)	0·0001*
sCD163, ng/mL	289 (207–419)	249 (181–343)	0·0001*
I-FABP, ng/mL	2·2 (1·5–3·7)	1·1 (0·7–1·6)	0·0001*
Markers of dyslipidaemia			
HDL, mmol/L	1·28 (1·02–1·57)	1·38 (1·13–1·67)	0·0001**
LDL, mmol/L	3·09 (2·45–3·69)	3·26 (2·64–3·84)	0·0025**
Total cholesterol, mmol/L	5·32 (4·62–6·01)	5·46 (4·85–6·08)	0·039**
Total cholesterol to HDL ratio	1·69 (1·55–1·94)	1·66 (1·54–1·81)	0·0033**
Triglycerides, mmol/L	1·63 (1·06–2·60)	1·43 (0·96–2·11)	0·0001*

Data are n (%) or median (IQR). Baseline characteristics were compared between HIV-positive and HIV-negative participants. Missing data were not considered in the comparisons. CES-D=Center for Epidemiologic Studies Depression Scale. hsCRP=highly sensitive C-reactive protein. I-FABP=intestinal-fatty-acid-binding protein. IL-6=interleukin-6. MSM=men who have sex with men. Non-MSM=men who do not have sex with men. sCD14=soluble CD14. sCD163=soluble CD163. *Wilcoxon rank-sum test. †Pearson $\chi 2$ test. ‡Male participants who stated in the questionnaire that they had had sex with ≥2 male sex partners in their lifetime. §Higher education means the individual has attained at least a bachelor's degree. ¶Heavy daily alcohol use is defined as >5 alcohol units every day for a man and >4 alcohol units every day for a woman during the 6 months preceding study enrolment. ||Binge alcohol drinking is defined as >6 alcohol units a day at least once per month during the 6 months preceding study enrolment. **Student's *t* test. ††Comorbidities are described (appendix 2 p 3). ‡‡Hypertension grade 2 is defined as diastolic blood pressure ≥100 mm/Hg or systolic blood pressure ≥160 mm/Hg in all three measurements within a 1-min interval, or on antihypertensive medication. §§Fried frailty phenotype classifies individuals as robust (0 points), prefrail (1–2 points), or frail (3–5 points).

Table 1: **Baseline characteristics of the 1146 participants in the AGE$_h$IV cohort at time of enrolment (2010–12) by HIV status**

between HIV status and time to obtain HIV-specific estimates of relative changes in mean total comorbidities over time. We excluded observations with missing data and no imputation of missing data was done. We report these adjusted estimates as the rate ratio (RR) in mean comorbidities per year. To assess if changes in mean total comorbidities over time were different between HIV-positive and HIV-negative participants, we tested an interaction term between HIV status and time using a z-test. The hazard of death was assumed to occur as an exponentially distributed survival function and was jointly modelled with a parametric survival model. For this model, we modelled the time to exact date of death for participants who were deceased or the time to date of lost to follow-up or to fourth study visit for participants who were not deceased. We included the submodel of total comorbidity count to estimate the hazard ratio (HR) and 95% CI of this count for death. Drop-out was assumed to be an interval-censored observation, the hazard of which was also modelled with a parametric survival model. If an individual was invited to a study visit but chose to withdraw or did not respond after three attempts to contact them, we decided that loss to follow-up had occurred at the first unattended visit. Every visit with available data was used in this model. We included the submodel of total comorbidity count to estimate the HR and 95% CI of this count for dropout. The multiple survival models allowed for estimation of death-specific HRs while accounting for censoring. Parameters from the three models were jointly estimated via maximum likelihood with the merlin program in Stata.[15]

We calculated DALYs at enrolment and during follow-up as they accrued within 24-month intervals until date of death, dropout, or fourth study visit (whichever occurred first). The distribution of DALYs had an excess of zero values and DALY values above zero had a distribution skewed to the right. Accordingly, we modelled having DALYs larger than zero and continuous DALYs with an exponential hurdle model.[16] We included HIV status, age at inclusion, continuous time, and the interaction between HIV status and time as covariates to obtain HIV-specific estimates of relative changes in mean DALYs over time. We excluded observations with missing data or for which DALYs could not be calculated, and no imputation of missing data was done. We report adjusted estimates of the relative change in DALYs per year. To assess if changes in mean DALYs during follow-up were different between HIV-positive and HIV-negative participants, we tested the HIV status and time interaction term using a z-test.

Major contributors to comorbidity development in people with HIV include having had severe immunosuppression or AIDS and having used toxic antiretroviral agents in the past.[6,17] Therefore, we did sensitivity analyses in which people with HIV were stratified by previous severe immunodeficiency (ie, nadir CD4 counts <200 cells per μL), history of AIDS, and previous use of the nucleoside-analogue reverse transcriptase inhibitors (NRTIs) didanosine, stavudine, and zalcitabine (hereafter referred to as toxic NRTIs).[18] Because of the strong influence of years of life lost on total DALYs, we did an additional sensitivity analysis in which years of life lost were excluded from the DALY calculation.

Significance was defined as a two-sided p<0·05. All analyses were done with Stata 15.1.

Role of the funding source

None of the study funders had a role in the study design, conduct of the study, analysis and interpretation of data, writing of the report, or decision to publish.

Results

596 HIV-positive and 550 HIV-negative participants were enrolled into the AGE$_h$IV study between Oct 29, 2010, and Oct 9, 2012, and were then prospectively followed up until their last visit before Oct 1, 2018. (table 1, appendix 2 p 16). 2161 individuals were screened for eligibility (ie, 1025 HIV-positive and 1136 HIV-negative) and, of these, 1148 individuals were enrolled (598 HIV-positive and 550 HIV-negative). Two enrolled HIV-positive individuals withdrew consent before their baseline visit. 95·8% of HIV-positive participants used antiretroviral treatment; 95·6% of those had HIV RNA viral loads less than 40 copies per mL in the year before enrolment. 363 (60·9%) of 596 HIV-positive participants had a mean CD4 count of larger than 500 cells per µL in the 12 months before enrolment; median nadir CD4 count was 170 cells per µL (table 2).

Median follow-up was 5·9 years (IQR 5·7–6·0) in HIV-positive participants and 5·9 years (5·8–6·0) in HIV-negative participants. During follow-up, seven HIV-negative participants became HIV positive, after which they were considered as HIV positive in analysis. HIV-positive participants missed 128 (5·7%) of 2097 visits and HIV-negative participants missed 117 (5·7%) of 2045 (p=0·60). During follow-up, HIV-positive participants were virally suppressed at 1852 (95·3%) of 1943 of study visits with available data. Five individuals had detectable HIV RNA at all study visits.

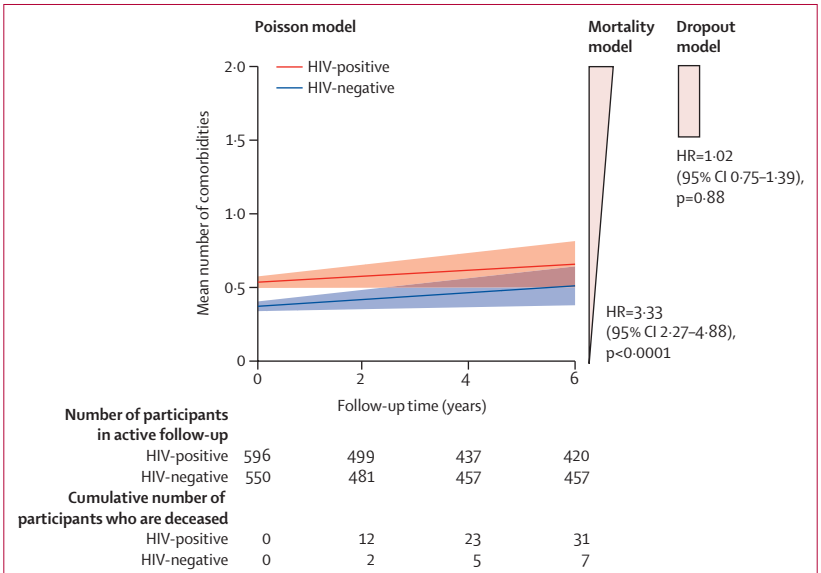
At cohort enrolment, 265 HIV-positive participants (44·5%) had one or more comorbidities compared with 142 HIV negative participants (25·8%; p<0·0001); 90 HIV-positive participants (15·1%) had two or more compared with 24 HIV-negative participants (4·4%; p<0·0001). Accordingly, the mean number of comorbidities per individual was 0·65 (95% CI 0·58–0·72) in HIV-positive participants and 0·32 (95% CI 0·27–0·37) in HIV-negative participants (p<0·0001). The most common comorbidities present at enrolment among the total study population were kidney disease (192 of 1146, 16·8%), osteoporosis (110 of 1146, 9·6%), and COPD (107 of 1146, 9·3%); kidney disease and osteoporosis were significantly more prevalent in HIV-positive participants than in HIV-negative participants (appendix 2 p 11).

From inclusion to end of follow-up, there were 1437 study-assessed and 421 self-reported comorbidities. Of the self-reported comorbidities, 218 (51·8%) could be validated: 155 (59·2%) of 262 in HIV-positive participants and 63 (39·6%) of 159 in HIV-negative participants (p=0·0001). 14 (2·5%) of 550 HIV-negative participants did not consent to contacting their general practitioner for validation. Similar increases in mean number of comorbidities were observed over time in both HIV-positive (RR 1·04, 95% CI

	n (%) or median (IQR)
Years since HIV diagnosis	12·0 (6·6–17·1)
CD4 cell count	
Nadir CD4 count, cells per µL	170 (70–260)
Mean CD4 in 12 months before enrolment, cells per µL	565
CD4/CD8 ratio at enrolment	0·70 (0·50–0·98)
History of AIDS diagnosis	192/596 (32·2%)
Taking combination ART at enrolment	571/596 (95·8%)
Cumulative exposure to ART, years	10·3 (4·4–14·5)
ART experienced before starting cART	120/571 (21·0%)
Ever taken toxic NRTIs	270/596 (45·3%)
Stavudine	215/596 (36·1%)
Didanosine	169/596 (28·4%)
Zalcitabine	57/596 (9·6%)
Duration of stavudine, years*	3·5 (1·6–5·5)
Duration of didanosine, years†	2·7 (0·9–6·9)
Duration of zalcitabine, years‡	0·7 (0·4–1·5)
HIV RNA <40 copies per mL in 12 months before enrolment§	543/593 (95·6%)
Cumulative duration of HIV RNA <200 c/mL, years§	8·7 (3·9–12·6)

Data are n (%) or median (IQR). ART=antiretroviral treatment. cART=combination ART. NRTIs=nucleoside-analogue reverse transcriptase inhibitors. *If ever taken stavudine. †If ever taken didanosine. ‡If ever taken zalcitabine. §If currently taking cART.

Table 2: **Characteristics of 596 HIV-positive participants in the AGE$_h$IV cohort at the time of enrolment (2010–12)**



Number of participants in active follow-up				
HIV-positive	596	499	437	420
HIV-negative	550	481	457	457
Cumulative number of participants who are deceased				
HIV-positive	0	12	23	31
HIV-negative	0	2	5	7

Figure 1: **Mean number of comorbidities developed per year of follow-up**
Results from the joint model when adjusting for mortality and dropout during the observation period of participants from the AGE$_h$IV cohort study. Thick lines show mean outcome. Shaded areas show 95% CIs. HRs for mortality and dropout are shown here per one-unit increase of the comorbidity model. HR=hazard ratio.

1·00–1·08) and HIV-negative participants (1·05, 1·01–1·08; figure 1) without significant differences between groups ($p_{interaction}$=0·78). The period prevalence over time for individual comorbidities has been described (appendix 2 p 18). There were similar increases in mean number of comorbidities when stratifying HIV-positive participants by previous severe immunodeficiency, history of AIDS, and previous use of toxic NRTIs (appendix 2 p 19). HIV-positive participants with previous severe immunodeficiency, AIDS, and previous use of toxic NRTIs had more ageing-associated comorbidities than did HIV-positive participants without these characteristics at any point during follow-up. Each additional comorbidity was associated with an increased hazard of death, but not with dropout (HR 3·33 per additional comorbidity, 95% CI 2·27–4·88, p<0.001; figure 1).

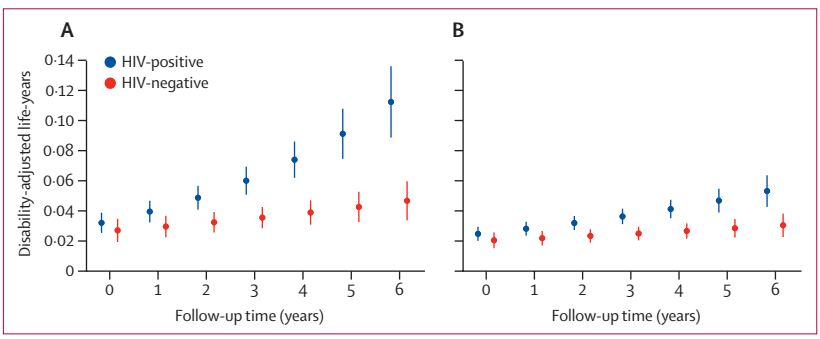


Figure 2: **Mean disability-adjusted life-years development over time**
Stratified by HIV status and adjusted for age at enrolment of participants from the AGE_nIV cohort study.

	HIV positive (n=31)	HIV negative (n=7)
Non-AIDS-defining malignancy	15	1
Gastrointestinal	5	0
Lung	4	1
Haematological	2	0
Breast	1	0
Melanoma	1	0
Anal	1	0
Missing	1	0
AIDS-defining malignancy	0	0
Organ failure or multiorgan failure	5	0
Cardiovascular disease	4	1
Overdose	1	0
Suicide	3	3
Missing	3	2

Causes of death were reported by the treating HIV doctor or the study doctor, as well as the participant's general practitioner, by use of the Coding Causes of Death form. AIDS-defining malignancies are Kaposi sarcoma, aggressive B-cell non-Hodgkin lymphoma, and cervical cancer. All other cancers were non-AIDS-defining malignancies. Organ failure or multiorgan failure as a cause of death included all organ dysfunction excluding malignancies and cardiovascular disease. Cardiovascular disease included myocardial infarction, peripheral artery disease, ischaemic and haemorrhagic stroke, or heart failure.

Table 3: **Causes of death among participants of the AGE_nIV cohort by HIV status**

At enrolment, median DALYs during the previous 24 months were low in both groups, but significantly higher in HIV-positive participants than in HIV-negative participants. 368 (61·7%) of 596 HIV-positive participants versus 436 (79·3%) of 550 HIV-negative participants (p<0·0001) had zero DALYs during the 24 months before enrolment. Among the participants with DALYs at enrolment, HIV-positive participants had a mean of 0·020, (95% CI 0·015–0·025) and HIV-negative participants had a mean of 0·019 (0·012–0·025; p=0·82). During follow-up, HIV-positive participants had higher increases in mean DALYs (0·209 per year, 95% CI 0·162–0·256) than HIV-negative participants (0·091 per year, 0·025–0·157; $p_{interaction}$=0·005; figure 2). When excluding years of life lost from the DALY estimate, the change in mean DALYs was not significantly different between HIV-positive (0·127, 0·083–0·171) and HIV-negative (0·066, 0·005–0·127; $p_{interaction}$=0·11) participants.

The increase in DALYs in HIV-positive participants with a nadir CD4 count of larger than 200 cells per µL (0·185, 95% CI 0·105–0·264) was not significantly different compared with HIV-negative participants (0·091, 0·025–0·157; $p_{interaction}$=0·075). By contrast, the increase in DALYs in HIV-positive participants with nadir CD4 counts less than 200 cells per µL (0·221, 0·163–0·279) was significantly faster than in HIV-negative participants (0·091, 0·025–0·157; $p_{interaction}$=0·0039; appendix 2 p 21). In HIV-positive participants both with (0·244, 0·168–0·320) and without (0·189, 0·129–0·248) a history of AIDS, the increase in DALYs was significantly faster than in HIV-negative participants (0·091, 0·025–0·157; $p_{interaction}$=0·0030 for HIV-positive participants with a history of AIDS and $p_{interaction}$=0·032 for HIV-positive participants without a history of AIDS; appendix 2 p 22). In HIV-positive participants who had never used toxic NRTIs, the DALY increase (0·173, 0·104–0·243) was not significantly different from HIV-negative participants (0·091, 0·025–0·157; $p_{interaction}$=0·093). The increase in DALYs in HIV-positive participants who had used toxic NRTIs (0·240, 0·178–0·303) was significantly faster than in HIV-negative participants (0·091, 0·025–0·157, $p_{interaction}$=0·0014; appendix 2 p 21).

38 (3·3%) of 1146 included participants died; 31 (5·2%) HIV-positive participants and seven (1·3%) HIV-negative participants. Of the 38 deceased participants, nine had no comorbidities at their previous study visits, 14 had one, and 15 had two or more. Among the 31 deaths in HIV-positive participants, none were AIDS-related but 24 were comorbidity-related. Of the seven deaths among HIV-negative participants, two were comorbidity-related (table 3). The median age of HIV-positive participants who died was higher than in HIV-positive participants who did not die; HIV-positive participants who died also had more pack years of smoking and were more frail (table 4). Furthermore, HIV-positive participants who died had lower mean nadir CD4 count at enrolment and more often

had a history of AIDS and use of toxic NRTIs (table 4). Deceased HIV-positive participants and deceased HIV-negative participants had similar age, smoking status, and frailty; however, prevalence of cytomegalovirus co-infection and levels of LDL cholesterol and total cholesterol were higher in deceased HIV-positive participants (table 4). During the study period, 231 (20·2%) participants dropped out; 145 (24·3%) of 596 HIV-positive participants and 86 (15·6%) of 550 HIV-negative participants. 103 (71·0%) of 145 and 51 (59·3%) of 86 withdrew consent and 42 (29·0%) of 145 and 35 (40·7%) of 86 were lost to follow-up.

Discussion

In this prospective, longitudinal cohort study, we showed that HIV-positive participants aged 50–55 years at the

	Surviving HIV-positive participants (n=565)	Deceased HIV-positive participants (n=31)	Deceased HIV-negative participants (n=7)	p value deceased *vs* surviving HIV-positive participants	p value deceased HIV-positive *vs* deceased HIV-negative participants
Demographics					
Age, years	53 (48–59)	59 (51–66)	60 (58–64)	0·0034*	0·59*
Male sex at birth	492 (87·1%)	30	7	0·11†	0·63†
Missing	0	0	0	..	..
Sexual behaviour in men	..	..	..	0·014†	0·78†
MSM‡	390/492 (79·3%)	17	3	..	..
Non-MSM	75/492 (15·2%)	9	3	..	..
Missing	27/492 (5·5%)	4	1	..	..
Ethnicity	..	..	..	0·52†	0·90†
Other than White	69 (12·2%)	5	1	..	..
White	496 (87·8%)	26	6	..	..
Missing	0 (0%)	0	0	..	..
Higher education§	214 (37·9%)	6	2	0·061†	0·67†
Missing	57 (10·1%)	6	2	..	..
Behavioural characteristics					
Smoking status	..	..	..	0·10†	0·99†
Never smoked	173 (30·6%)	5	1	..	..
Former smoker	183 (32·4%)	8	2	..	..
Current smoker	161 (28·5%)	13	3	..	..
Missing	48 (8·5%)	5	1	..	..
Pack years if ever smoked	20·1 (7·3–35·2)	35·0 (27·1–53·0)	31·9 (16·4–47·1)	0·0021*	0·54*
Alcohol use	..	..	..	0·026†	0·79†
Never	48 (8·5%)	3	0	..	..
Former drinker	76 (13·5%)	6	1	..	..
Current drinker	414 (73·3%)	17	5	..	..
Missing	27 (4·8%)	5	1	..	..
Heavy daily alcohol use in the past 6 months¶	17 (3·0%)	1	1	0·58†	0·50†
Missing	58 (10·3%)	5	1	..	..
Binge alcohol drinking during the past 6 months‖	109 (19·3%)	1	2	0·0087†	0·074†
Missing	74 (13·1%)	9	1	..	..
Any injection drug use	18 (3·2%)	1	1	0·10†	0·47†
Missing	58 (10·3%)	7	1	..	..
Tetrahydrocannabinol use in the 6 months preceding study enrolment	69 (12·2%)	3	0	0·091†	0·57†
Missing	57 (10·1%)	7	1	..	..
Body composition					
Waist circumference, cm	93·4 (86·3–100·1)	95·0 (88·4–102·3)	99·4 (91·9–109·3)	0·23**	0·35**
Hip circumference, cm	96·3 (92·1–100·9)	98·1 (92·0–100·5)	97·4 (96·0–111·4)	0·80**	0·42**
Waist to hip ratio	0·97 (0·91–1·01)	0·99 (0·93–1·04)	0·98 (0·96–1·05)	0·059**	0·87**
BMI, kg/m²	24·2 (22·4–26·7)	26·0 (22·1–27·4)	26·8 (22·9–31·5)	0·37**	0·32**

(Table 4 continues on next page)

	Surviving HIV-positive participants (n=565)	Deceased HIV-positive participants (n=31)	Deceased HIV-negative participants (n=7)	p value deceased *vs* surviving HIV-positive participants	p value deceased HIV-positive *vs* deceased HIV-negative participants
(Continued from previous page)					
Comorbidity					
Number of ageing-associated comorbidities	..	..	..	..	..
0	320 (56·6%)	11	2	<0·0001†	0·39†
1	166 (29·4%)	9	4	..	..
2	61 (10·8%)	4	1	..	..
≥3	18 (3·2%)	7	0	..	..
Hypertension grade 2††	148 (26·2%)	8	3	0·96†	0·37†
Hepatitis B virus DNA-positive	34 (6·0%)	4	0	0·45†	0·29†
Hepatitis C virus RNA-positive	19 (3·4%)	2	0	0·30†	0·086†
Cytomegalovirus IgG-positive	534 (94·5%)	29	4	0·82†	0·010†
Depressive symptoms					
CES-D ≤8	266 (47·1%)	12	3	0·28†	0·47†
CES-D 8–16	123 (21·8%)	5	2	..	..
CES-D ≥16	121 (21·4%)	8	0	..	..
Missing	55 (9·7%)	6	2	..	..
Fried frailty phenotype‡‡					
Robust	209 (37·0%)	5	2	0·0014†	0·47†
Prefrail	294 (52·0%)	18	2	..	..
Frail	61 (10·8%)	7	3	..	..
Missing	1 (0·2%)	1	0	..	..
Markers of inflammation					
hsCRP, mg/L	1·5 (0·7–3·3)	2·8 (1·2–5·8)	1·7 (0·6–4·3)	0·024*	0·29*
D-dimer, mg/L	0·22 (0·20–0·34)	0·29 (0·20–0·53)	0·40 (0·24–0·96)	0·014*	0·46*
IL-6, pg/mL	1·5 (1·0–2·9)	1·6 (1·1–2·6)	1·8 (1·1–3·1)	0·56*	0·90*
sCD14, ng/mL	1579 (1291–2010)	1631 (1400–1951)	1356 (1139–1734)	0·25*	0·057*
sCD163, ng/mL	286 (207–417)	341 (238–582)	427 (303–536)	0·067*	0·40*
I-FABP, ng/mL	2·2 (1·5–3·7)	2·0 (1·4–3·3)	1·4 (1·0–2·1)	0·85*	0·15*
Markers of dyslipidaemia					
HDL, mmol/L	1·29 (1·01–1·58)	1·23 (1·05–1·44)	1·21 (1·06–1·28)	0·49	0·87
LDL, mmol/L	3·06 (2·44–3·69)	3·24 (2·89–4·04)	1·63 (1·42–3·38)	0·14	0·033
Total cholesterol, mmol/L	5·30 (4·60–6·01)	5·35 (4·85–6·37)	3·29 (2·87–5·44)	0·21	0·033
Total cholesterol/HDL ratio	1·69 (1·55–1·94)	1·69 (1·49–1·80)	1·78 (1·60–2·32)	0·38	0·22
Triglycerides, mmol/L	1·62 (1·06–2·57)	1·76 (1·19–3·13)	1·49 (0·64–2·10)	0·34	0·27

(Table 4 continues on next page)

time of enrolment had consistently higher mean numbers of comorbidities at all timepoints during 6 years of follow-up than did HIV-negative participants, but without a difference in the rate at which these increased. Having a higher number of comorbidities overall was strongly associated with increased risk of dying, but not with dropping out of the study. The burden of living with comorbidity in terms of DALYs was higher in people with HIV at enrolment, and DALYs increased more rapidly over time in HIV-positive participants than in HIV-negative participants. The increase in DALYs was largely explained by a higher rate of comorbidity-associated mortality in HIV-positive participants, with a large proportion of deaths being related to non-AIDS malignancies.

Similar to our findings, a retrospective, population-based cohort study from Denmark showed that the annual prevalence of several ageing-associated comorbidities was higher in people with HIV than in people without HIV, with the change over time being similar to the change in HIV-negative control individuals.[4] Similar findings were reported by studies that focused on a single comorbidity and had shorter periods of follow-up than our study.[19,20]

Our burden of disease analysis showed a more rapid increase in DALYs in people with HIV, primarily due to increased mortality associated with various comorbidities, mostly non-AIDS malignancies. This increase in DALYs was observed most in people with HIV with low nadir CD4 counts or exposure to toxic NRTIs. None of the

	Surviving HIV-positive participants (n=565)	Deceased HIV-positive participants (n=31)	Deceased HIV-negative participants (n=7)	p value deceased *vs* surviving HIV-positive participants	p value deceased HIV-positive *vs* deceased HIV-negative participants
(Continued from previous page)					
HIV-related variables					
Years since HIV diagnosis	12·0 (6·2–17·1)	13·3 (9·2–17·5)	..	0·29**	..
CD4 cell count	..	..	..	..	..
Nadir CD4 count, cells per μL	180 (80–260)	80 (40–170)	..	0·0017*	..
Mean CD4 in the 12 months before enrolment, cells per μL	570	530	..	0·18*	..
CD4/CD8 ratio at enrolment	0·71 (0·50–0·99)	0·60 (0·46–0·77)	..	0·038*	..
History of AIDS diagnosis	176 (31·2%)	16 (51·6%)	..	0·018†	..
Taking cART at enrolment	540 (95·6%)	31 (100%)	..	0·23**	..
Cumulative exposure to antiretroviral treatment, years	10·1 (4·2–14·4)	12·6 (7·8–15·7)	..	0·038*	..
ART experienced before starting cART	109 (20·2%)	11 (35·5%)	..	0·042†	..
Ever taken toxic NRTIs	250 (44·3%)	20 (64·5%)	..	0·027†	..
Stavudine	200 (35·4%)	15 (48·4%)	..	0·14†	..
Didanosine	157 (27·8%)	12 (38·7%)	..	0·19†	..
Zalcitabine	54 (9·6%)	3 (9·7%)	..	0·98†	..
Duration of stavudine, years§§	3·5 (1·5–5·5)	4·4 (2·8–5·4)	..	0·54*	..
Duration of didanosine, years¶¶	2·7 (1·0–7·0)	1·4 (0·5–4·2)	..	0·25*	..
Duration of zalcitabine, years||||	0·7 (0·4–1·5)	0·6 (0·1–0·7)	..	0·30*	..
HIV RNA <40 c/mL in the 12 months before enrolment***	514 (91·5%)	29 (93·6%)	..	0·68†	..
Cumulative duration of HIV RNA <200 copies per mL, years***	8·6 (3·7–12·5)	12·2 (6·6–12·7)	..	0·038*	..

Data are n (%), n, or median (IQR). Baseline characteristics were compared between deceased HIV-positive participants and HIV-positive participants who are not deceased and between deceased HIV-positive participants and deceased HIV-negative participants. Missing data were not considered in the comparisons. ART=antiretroviral treatment. cART=combination ART. CES-D=Center for Epidemiologic Studies Depression Scale. hsCRP=highly sensitive C-reactive protein. I-FABP=intestinal-fatty-acid-binding protein. IL-6=interleukin-6. MSM=men who have sex with men. Non-MSM=men who do not have sex with men. NRTIs=nucleoside-analogue reverse transcriptase inhibitors. sCD14=soluble CD14. sCD163=soluble CD163. *Wilcoxon rank-sum test. †Pearson $\chi 2$ test. ‡Male participants who stated in the questionnaire that they had had sex with ≥2 male sex partners in their lifetime. §Higher education means the individual has attained at least a bachelor's degree. ¶Heavy daily alcohol use is defined as >5 alcohol units every day for a man and >4 alcohol units every day for a woman during the 6 months preceding study enrolment. ||Binge alcohol drinking is defined as >6 alcohol units a day at least once per month during the 6 months preceding study enrolment. **Student's *t* test. ††Hypertension grade 2 is defined as diastolic blood pressure ≥100 mm/Hg or systolic blood pressure ≥160 mm/Hg in all three measurements within a 1-min interval, or on antihypertensive medication. ‡‡Fried frailty phenotype classifies individuals as robust (0 points), prefrail (1–2 points), or frail (3–5 points). §§If ever taken stavudine. ¶¶If ever taken didanosine. ||||If ever taken zalcitabine. ***If currently taking cART.

Table 4: **Baseline characteristics of the 31 deceased HIV-positive participants compared with the 565 surviving HIV-positive participants and the seven deceased HIV-negative participants of the AGE$_n$IV cohort study**

participants died from AIDS-related causes. Large cohort studies have shown non-AIDS-defining malignancies to be an important cause for morbidity and mortality in people with HIV[17,21] and to be associated with increased age, low CD4 cell count nadir, extended periods of untreated HIV infection, and previous use of toxic NRTIs. Our data might offer support to the concept that HIV-infection-induced severe immune deficiency and previous exposure to toxic NRTIs could result in an accentuation of ageing (ie, there was a point before follow-up at which these events led to an increased risk of comorbidities), but that this accentuation does not increase over time after virological suppression.

To what extent past exposure to toxic NRTIs has long-term, oncogenic potential remains unclear.[22,23] Moreover, distinguishing their effect from that of previous periods of suboptimal HIV suppression, increased systemic inflammation, and advanced immune deficiency is challenging.

Our results have important consequences for clinical care and prevention strategies, and they bring awareness of comorbidities to both people with HIV and HIV doctors alike. Having comorbidities comes with disability, risk of polypharmacy, and risk of premature mortality. Despite awareness about the increased risk of comorbidities, uptake of preventive strategies is not

optimal and should be improved, such as for cardiovascular risk management.[24] None of the cancer screening programmes, except those concerning anogenital cancers, include indications for increased screening in people with HIV, despite increasing evidence for increased cancer risk in these individuals.

The strengths of our study are its longitudinal, prospective design and the extensive and standardised data collection, including careful validation of self-reported comorbidities, in both HIV-positive and HIV-negative participants, which was similar with regard to most lifestyle and demographic factors. However, our study also has some limitations. First, there were differences in the proportion of individuals with and without HIV who reported ever being screened for specific types of cancers, indicating a potential differential screening bias. However, rates of cervical cancer, anal cancer, and breast cancer were low in this study, even in the groups with more active cancer screening. Therefore, the influence of such a bias is likely to be minimal. Second, as most of our HIV-positive participants had been diagnosed with HIV many years before enrolment and many had had severe immunodeficiency or AIDS, our results might not be generalisable to participants who are diagnosed more quickly after HIV acquisition and start antiretroviral treatment immediately with contemporary regimens. Third, there was a higher proportion of non-validated, self-reported comorbidities in people without HIV than in people with HIV. Assuming that non-validated comorbidities were misclassified, the differences in comorbidity counts and DALYs could be larger than we observed. Fourth, several comorbidities, such as liver disease, mental ill health, and comorbidities related to endocrine disorders other than diabetes, were not considered in analysis, mainly owing to the lack of sufficient data needed to calculate the DALY. Inclusion of these comorbidities could alter our findings. Fifth, we chose a parsimonious submodel of comorbidities with few covariates. Including sex, ethnicity, and smoking status in this submodel did not substantially modify our results (appendix 2 p 23). However, there were other covariates, notably social determinants of health, for which we were unable to account. Finally, our cohort consisted mainly of White men who have sex with men and individuals who are linked to care. Our results might not be generalisable to other important populations, such as individuals who encounter barriers to health-care access through stigma or otherwise and women in other countries.

In conclusion, the comorbidity prevalence in people with HIV on effective antiretroviral treatment who were aged 50–55 years at cohort entry remained consistently larger than in HIV-negative control individuals and was associated with an increased risk of death. Although comorbidity prevalence increased similarly as participants aged, the disease burden attributed to comorbidities in terms of DALYs differed, mainly explained by years of life lost because of malignancy-related deaths. This increase in DALYs was largest in people with HIV with low nadir CD4 count or past exposure to toxic NRTIs. Our findings highlight the need for strategies to optimise prevention, screening, and early intervention for ageing-associated comorbidities and non-AIDS malignancies, particularly for long-term survivors with HIV as they age. Future research should focus on the implementation of these strategies, including their costs, to ensure care for an ageing population with HIV.

Contributors

All authors contributed to the conceptualisation and design of the study. EV, SOV, and MLV curated data and contributed to data collection and coordination of the study. EV and AB designed the methods of the study and did the formal data analysis. EV, SOV, and AB accessed and verified the underlying data. PR obtained funding and supervised the study. EV wrote the original draft of the manuscript, including figures. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

FWW has served on scientific advisory boards for ViiV Healthcare and Gilead Sciences. MFSvdL has served on advisory boards for Merck Sharp & Dohme. MvdV has served on advisory boards for Gilead Sciences; Merck, Sharp, & Dohme; and ViiV Healthcare. MvdV has received independent scientific grant support from Gilead Sciences; Merck, Sharp, & Dohme; and ViiV Heealthcare, all of which were paid to his institution (Amsterdam University Medical Centers, Amsterdam, Netherlands). PR has received independent scientific grant support from the Netherlands Organization for Health Research and Development (30002000), Gilead Sciences, ViiV Healthcare, Merck & Co, Aidsfonds (2009063), and Janssen Pharmaceuticals and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, Janssen Pharmaceuticals, and Merck & Co, all of which were paid to his institution. All other authors declare no competing interests.

Data sharing

Data sharing has been restricted by the Ethical Review Board of the Amsterdam University Medical Centers because the data underlying this study contain sensitive and potentially identifying information. Requests for data sharing can be made via submission of a concept sheet as per instructions on the project website (https://agehiv.nl/en/science/). Once submitted, the proposed research or analysis will undergo review for evaluation of the scientific value, relevance to the study, design and feasibility, statistical power, and overlap with existing projects. If the proposed analysis is for verification or replication, data will then be made available. If the proposed research is for novel science, feedback will be provided to the proposers upon completion of the review. In some circumstances, a revision of the concept can be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (ie, up to three individuals that were centrally involved in the development of the concept) and members of the AGE$_h$IV Cohort Study group or other appointed cohort representatives. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. Deidentified participant data, along with a data dictionary, will be made available if the concept is approved. Study protocol and blank informed consent forms can also be provided on request.

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