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Supplementary appendix 2

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Supplement to: Verheij E, Boyd A, Wit FW, et al. Long-term evolution of comorbidities and their disease burden in individuals with and without HIV as they age: analysis of the prospective AGE_hIV cohort study. *Lancet HIV* 2023; published online Feb 9. https://doi.org/10.1016/S2352-3018(22)00400-3.

Supplementary material to: Verheij E, Boyd A, Wit FW, et al. 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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SUPPLEMENTARY METHODS

Study Design and Data Collection

From Schouten J, Wit FW, Stolte IG, et al. Cross-sectional Comparison of the Prevalence of Age-Associated Comorbidities and Their Risk Factors Between HIV-Infected and Uninfected Individuals: The AGE$_h$IV cohort Study. CID 2014:59 (15 Dec):

> HIV-1–infected participants were recruited from the HIV outpatient clinic of the Academic Medical Center in Amsterdam, and HIV-uninfected participants (controls) were recruited from the sexual health clinic of the Amsterdam Public Health Service or among uninfected participants in the existing Amsterdam Cohort Studies on HIV/AIDS.[1] To ensure comparability of the HIV-infected and HIV- uninfected study groups, we regularly monitored age, sex, and ethnicity in both study groups, and adjusted enrolment of underrepresented categories among HIV-uninfected participants accordingly. All participants were aged ≥45 years with laboratory confirmed presence or absence of HIV-1 infection. All subjects who provided written informed consent within the 2-year enrolment period were included. Of 1100 eligible patients from the HIV outpatient clinic, between 600 and 800 were expected to be enrolled, and we therefore aimed to include a similar number of uninfected controls. This sample size would provide sufficient statistical power to investigate associations between a broad range of AANCCs and potential risk factors. At baseline, 2 years later, and depending on sufficient resources every 2 years thereafter, participants undergo standardized screening for AANCCs and organ dysfunction. Participants are requested to complete a standardized questionnaire concerning demographics, (family) medical history, use of medications (both prescribed and over-the-counter), participation in population screening programs, substance use, quality of life, depression, sexual orientation/behaviour/dysfunction, cognitive complaints, calcium/vitamin D intake, physical exercise, social behaviour, and work participation/income. All participants undergo measurements of blood pressure, height, weight, and hip/waist circumference, as well as electrocardiography, measurement of vascular elasticity, spirometry, screening cognitive tests, frailty, bone densitometry, and quantification of advanced glycation end products in the skin. Blood and urine samples are obtained for extensive laboratory testing, and cryopreserved for future analyses. Detailed information concerning HIV and ART history is obtained from the Dutch HIV Monitoring Foundation, formally responsible for capturing detailed HIV/ART-related data from all individuals in care for HIV at an HIV treatment facility in the Netherlands.[2] The study protocol was approved by the local ethics review committee and registered at www.clinicaltrials.gov (identifier NCT01466582). All participants provided written informed consent.

Cancer screening practices in the Netherlands

The Netherlands has national cancer screening recommendations for colon, breast, and cervical cancer. For colon cancer screening, individuals between the ages of 55 and 75 are asked to participate in a national, voluntary screening programme, which involves sending stool samples every two years for a faecal immunochemical test (https://www.rivm.nl/en/colorectal-cancer-screening-programme). However, colonoscopies are recommended for certain individuals at high risk of colorectal cancer (e.g., family history of colorectal cancer, etc. in Dutch: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/zakkaart-coloscopie-surveillance_t.b.v._website.pdf). For breast cancer, women between the ages of 55 and 75 are invited to receive a mammography (https://www.rivm.nl/en/breast-cancer-screening-programme). Screening for lung cancer is based on more specific guidelines (in Dutch: https://richtlijnendatabase.nl/richtlijn/niet_kleincellig_longcarcinoom/screening.html).
For cervical cancer screening, women in the general population between the ages of 30 and 60 are invited every 5 years for a pap-smear test (https://www.rivm.nl/en/cervical-cancer-screening-programme). Cervical cancer screening for women living with HIV is started at a younger age and is conducted more frequently. There are currently no formal Dutch national guidelines concerning screening for anal (pre-)cancer in men who have sex with men living with HIV, although several of the centres providing HIV care have implemented screening by high resolution anoscopy. The Dutch Association of HIV Treating Physicians (NVHB)'s guidelines for screening for anogenital malignancies largely follow those of the US Department of Health and Human Services (http://richtlijnhiv.nvhb.nl/index.php/Hoofdstuk_13._Screening_van_mensen_met_hiv_op_anogenitale_maligniteiten & https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/human-0?view=full).

Detailed description of comorbidities

Chronic obstructive pulmonary disease or asthma (having obstructive pulmonary disease if 1-second forced expiratory volume (FEV1) to forced vital capacity (FVC) ratio was <0·7 for 3 forced expiratory spirometric measurements (MicroDirect Spiro USB) and having an FEV1 lower than 80% of the predicted value [i.e., Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage ≥2] (https://goldcopdorg.)), diabetes (HbA1c ≥ 48 mmol/mol and/or elevated blood glucose (non-fasting ≥ 11·1 mmol/L or fasting ≥ 7·0 mmol/L) or on antidiabetic medication. If participants only had an elevated Hba1c or glucose and concomitantly used prednisolon but no antidiabetic medication, they were not classified as having diabetes), kidney disease (having an estimated glomular filtration rate (eGFR) <60 mL/min/1·73 m2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or albuminuria defined as urine albumine/creatinine ratio of ≥30mg/g following Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. HIV-positive participants meeting these criteria but who had started ARVs known to inhibit tubular secretion of creatinine (i.e. dolutegravir, bictegravir, rilpivirine and/or cobicistat) prior to the development of kidney disease were excluded), osteoporosis (having a T score of-2·5 SD or lower, in men aged <50 years and premenopausal women; a Z score of-2 SD or lower in men aged ≥50 years and postmenopausal women), self-reported and validated heart-failure, non-AIDS defining malignancies (excluding non-melanoma skin cancers), cardiovascular disease (myocardial infarction, angina pectoris, peripheral artery disease, ischemic or hemorrhagic stroke, and heart failure).

Calculating disability adjusted life year (DALY)

DALY is loosely defined as 'healthy' years of life lost. DALYs consist of Years Lost due to Disability (YLD) for participants living with a comorbidity or its consequences and Years of Life Lost (YLL) due to premature mortality. More specifically, it is calculated as:

$$DALY = YLD + YLL$$

where YLD = disability weight (DW using Global Burden of Disease Study (GBD) 2015 weights) * duration of the comorbidity and YLL = 1 * premature mortality in years.

YLD were the number of years living with a comorbidity weighted by a factor which takes into account the disability caused by the comorbidity over time (i.e. disability weights), according to criteria developed by the Global Burden of Disease Study (GBD) (Supplementary Table S1).[3] We calculated DALYs resulting from the following comorbidities: non-AIDS malignancies, congestive heart failure, myocardial infarction, angina pectoris, peripheral arterial disease, ischemic and haemorrhagic stroke, COPD, diabetes mellitus type II and kidney disease. As DALYs estimate the burden of disease and osteoporosis is often asymptomatic, we only included participants with self-reported fractures and documented osteoporosis by Dual-energy X-ray absorptiometry for the purpose of this analysis (Supplementary Table S1).

YLD were calculated as the product of the disability weight and the duration of (multi)morbidity (Supplementary Figure S2). The duration of the comorbidities depends on the type of comorbidity. We considered recurring MI, ischemic and haemorrhagic strokes, and osteoporotic fractures as separate events with additional disability. For malignancies, a subsequent different malignancy was considered a separate event with additional disability, but recurrence of the same malignancy was not. Sequelae and their duration for a malignancy and for an MI were handled according to GBD 2015 criteria (see Supplementary Table S1 for details). For self-reported comorbidities with acute manifestations (myocardial infarction, bone fracture), the duration is set to 30 days in total for myocardial infarction following GBD definitions and 12 weeks for bone fractures.[3] For comorbidities assessed at the study visits (COPD, diabetes mellitus, kidney disease), these comorbidities were considered chronic. Their duration starts one year before the study visit and stops one year before the next study visit if the comorbidity is then absent. PAD was considered to be chronic and was included in the analysis from date of diagnosis (< 24 months before enrolment) until the end of follow-up.

For years of life loss, we introduce the concept of "immortal" time for deceased participants as the follow-up time (including study visits) that would have occurred had the participant not died. For deceased participants, YLL would then be defined as the difference between the date of the immortal study visit (assuming two-year study visit intervals) and date of death, provided that the immortal age was less than the expected age of death (based on birth year). The expected age of death was set on 86·6 years for males and females according to the GBD 2015 reference life table.[4] Two examples of this calculation are illustrated in Supplementary Figure S3.

For all alive participants, YLL would be defined as zero. As they by definition had been alive during the 24 months prior to enrolment, they all received a value of zero at baseline.

Multiplicative approach

When more than one comorbidity was present, we used a multiplicative approach to calculate the combined disability weights[5]:

$$DW_{combined} = 1 - \prod_{C}^{c}(1 - DW_c)$$

where DW_c is the disability weight for comorbidity, *c*, for a total of *C* comorbidities.

The AGEhIV Cohort Study Group

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SUPPLEMENTARY TABLES

Supplementary Table S1. Linking comorbidities in AGEhIV to disability weights* (DW) as defined by the Global Burden of Disease study (GBD) in 2015.

Comorbidity	**Definition Comorbidity Count****	**Definition Comorbidity DALY*****	**Sequela as defined by the GBD 2015 study**	**Duration** [+]	**Disability weight as defined by the GBD 2015 study**[++]
Malignancy	Non-AIDS defining cancers (confirmed by pathologist, excluding non-melanoma skin cancers and pre-cancerous conditions) during any stage of the disease.	Non-AIDS defining cancers (confirmed by pathologist, excluding non-melanoma skin cancers and pre-cancerous conditions)	Diagnosis and primary therapy phase of cancer	1 year, from date of diagnosis	0·288 (0·193-0·399)
			Controlled phase of cancer	4 years	0·049 (0·031-0·072)
			Metastatic phase of cancer	From first date of diagnosed metastasis until the end of the last study visit, follow-up or death	0·451 (0·307-0·6)
			Terminal phase of cancer	From first date of palliative phase until end of the last study visit, follow-up or death·	0·540 (0·377-0·687)
Congestive heart failure	Diagnosed by cardiologist	Diagnosed by cardiologist	Severe heart failure	From first date of diagnosis until the end of the last study visit, follow-up or death	0·179 (0·122-0·251)
Myocardial infarction	Diagnosed by cardiologist	Diagnosed by cardiologist	Acute myocardial infarction first 2 days	For 2 days	0·432 (0·288-0·579)
			Acute myocardial infarction 3 to 28 days	For 28 days	0·074 (0·049-0·105)
Angina pectoris	Diagnosed by cardiologist	Diagnosed by cardiologist	Mild angina due to ischemic heart disease	From first date of diagnosis until the end of the last study visit, follow-up or death	0·033 (0·02-0·052)
Peripheral arterial disease	Diagnosed by specialist	Diagnosed by specialist	Symptomatic claudication due to peripheral vascular disease	From first date of diagnosis until the end of the last study visit, follow-up or death	0·014 (0·007-0·025)
Ischemic and hemorrhagic stroke	Diagnosed by neurologist	Diagnosed by neurologist	Chronic ischemic stroke severity level 1	From first date of diagnosis until the end of the last study visit, follow-up or death	0·019 (0·01-0·032)

Comorbidity	**Definition Comorbidity Count****	**Definition Comorbidity DALY*****	**Sequela as defined by the GBD 2015 study**	**Duration** [+]	**Disability weight as defined by the GBD 2015 study**[++]
Chronic Obstructive Pulmonary Disease (COPD)	Having obstructive pulmonary disease if 1-second forced expiratory volume (FEV1) to forced vital capacity (FVC) ratio was <0·7 for 3 forced expiratory spirometric measurements (MicroDirect Spiro USB) and having an FEV1 lower than 80% of the predicted value [i.e., Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage ≥2] (https://goldcopdorg.)	Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2: Having mild obstructive pulmonary disease if 1-second forced expiratory volume (FEV1) to forced vital capacity (FVC) ratio was <0·7 for 3 forced expiratory spirometric measurements (MicroDirect Spiro USB) and having 50% ≤ FEV1 < 80% than of the predicted value	Mild chronic obstructive pulmonary disease	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is already present at the previous study visit, then the duration of the disease starts at date of previous study visit	0·019 (0·011-0·033)
		Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3: Having moderate obstructive pulmonary disease if 1-second forced expiratory volume (FEV1) to forced vital capacity (FVC) ratio was <0·7 for 3 forced expiratory spirometric measurements (MicroDirect Spiro USB) and having 30% ≤ FEV1 < 50% than of the predicted value	Moderate chronic obstructive pulmonary disease	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is already present at the previous study visit, then the duration of the disease starts at date of previous study visit	0·225 (0·153-0·31)
		Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 4: Having severe obstructive pulmonary disease if 1-second forced expiratory volume (FEV1) to forced vital capacity (FVC) ratio was <0·7 for 3 forced expiratory spirometric measurements (MicroDirect Spiro USB) and having an FEV1 < 30% than of the predicted value	Severe chronic obstructive pulmonary disease without heart failure	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is already present at the previous study visit, then the duration of the disease starts at date of previous study visit	0·408 (0·273-0·556)
Diabetes Mellitus type II	Diabetes mellitus was defined as having an HbA1c ≥48 mmol/mol or elevated blood glucose (non-fasting ≥11·1 mmol/L or fasting ≥7·0 mmol/L) or taking antidiabetic medication. If participants only had an elevated Hba1c or glucose and concomitantly used prednisolon but no antidiabetic medication, they were not classified as having diabetes.	Diabetes mellitus was defined as having an HbA1c ≥48 mmol/mol or elevated blood glucose (non-fasting ≥11·1 mmol/L or fasting ≥7·0 mmol/L) or taking antidiabetic medication. If participants only had an elevated Hba1c or glucose and concomitantly used prednisolon but no antidiabetic medication, they were not classified as having diabetes.	Uncomplicated diabetes mellitus	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is already present at the previous study visit, then the duration of the disease starts at date of previous study visit	0·049 (0·031-0·072)

Comorbidity	Definition Comorbidity Count**	Definition Comorbidity DALY***	Sequela as defined by the GBD 2015 study	Duration +	Disability weight as defined by the GBD 2015 study++
Kidney disease	Having an estimated glomular filtration rate (eGFR) <60 mL/min/1·73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or albuminuria defined as urine albumin/creatinine ratio of ≥30mg/g following Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. HIV-positive participants meeting these criteria but who had started ARVs known to inhibit tubular secretion of creatinine (i.e. dolutegravir, bictegravir, rilpivirine and/or cobicistat) prior to the development of kidney disease were not considered to have kidney disease.	Moderate : (eGFR ≥30 < 45 ml/min/1·73 m2 with albuminuria/creatinine ratio <30 mg/g or eGFR ≥ 45 < 60 ml/min/1·73 m2 with albuminuria/creatinine ratio 30 – 300 mg/g or eGFR ≥ 60 ml/min/1·73 m2 with albuminuria/creatinine ratio >300 mg/g). HIV-positive participants meeting these criteria but who had started ARVs known to inhibit tubular secretion of creatinine (i.e. dolutegravir, bictegravir, rilpivirine and/or cobicistat) prior to the development of kidney disease were not considered to have kidney disease..	Stage III chronic kidney disease and mild anaemia	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is measured already at enrolment, then the duration of the disease starts at date of first study visit	0·004 (0·001-0·008)
		Severe (eGFR ≥30 < 45 ml/min/1·73 m2 with albuminuria/creatinine ratio <30 mg/g or eGFR < 30 ml/min/1·73 m2 with albuminuria/creatinine ratio <30 mg/g or eGFR < 45 ml/min/1·73 m2 with albuminuria/creatinine ratio 30-300 mg/g or eGFR < 60 ml/min/1·73 m2 with albuminuria/creatinine ratio >300 mg/g). HIV-positive participants meeting these criteria but who had started ARVs known to inhibit tubular secretion of creatinine (i.e. dolutegravir, bictegravir, rilpivirine and/or cobicistat) prior to the development of kidney disease were not considered to have kidney disease.	Stage IV chronic kidney disease without anaemia	The duration starts one year before the study visit and stops one year before the next study visit if the disease is then absent. Unless the disease is already present at the previous study visit, then the duration of the disease starts at date of previous study visit	0·104 (0·07-0·147)
Osteoporosis	Osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan. (DXA scans were not available for the fourth study visit)	When having had a fracture of the clavicle, scapula or humerus within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of clavicle, scapula or humerus (short or long term, with or without treatment)	12 weeks	0·035 (0·021-0·053)
		When having had a fracture of the face bone within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World	Fracture of face bone (short or long term, with or without treatment)	12 weeks	0·067 (0·044-0·097)

Comorbidity	Definition Comorbidity Count**	Definition Comorbidity DALY***	Sequela as defined by the GBD 2015 study	Duration [+]	Disability weight as defined by the GBD 2015 study[++]
		Health Organization definitions or on bisphosphonates in the absence of a DXA scan			
		When having had a fracture of the foot bones within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of foot bones (short term, with or without treatment)	12 weeks	0·026 (0·015-0·043)
		When having had a fracture of the hand bones within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of hand (short term, with or without treatment)	12 weeks	0·010 (0·005-0·019)
		When having had a fracture of the neck of the femur within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of neck of femur (long term, with treatment)	12 weeks	0·058 (0·038-0·084)
		When having had a fracture of the femur, other than femoral neck, within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture, other than femoral neck (short term, with or without treatment)	12 weeks	0·111 (0·074-0·156)
		When having had a fracture of the patella, tibia or fibula or ankle within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-	Fracture of patella, tibia or fibula or ankle (short term, with or without treatment)	12 weeks	0·050 (0·032-0·075)

Comorbidity	Definition Comorbidity Count**	Definition Comorbidity DALY***	Sequela as defined by the GBD 2015 study	Duration [+]	Disability weight as defined by the GBD 2015 study[++]
		menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan			
		When having had a fracture of the pelvis within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of pelvis (short term)	12 weeks	0·279 (0·188-0·384)
		When having had a fracture of the radius or ulna within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of radius or ulna (short term, with or without treatment)	12 weeks	0·028 (0·016-0·046)
		When having had a fracture of the sternum and/or fracture of the ribs within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of sternum and/or fracture of one or two ribs (short term, with or without treatment)	12 weeks	0·103 (0·068-0·145)
		When having had a fracture of the vertebral column within 2 years' time of a diagnosis with osteoporosis (Dual-energy X-ray absorptiometry [DXA] T-score <-2·5 standard deviation (SD) for men aged ≥50 years and post-menopausal women or a Z-score <-2·0 for men aged <50 years and pre-menopausal women using World Health Organization definitions or on bisphosphonates in the absence of a DXA scan	Fracture of vertebral column (short or long term, with or without treatment)	12 weeks	0·111 (0·075-0·156)

*Malignancies, heart failure, myocardial infarction, angina pectoris, peripheral arterial disease and ischemic and haemorrhagic stroke were evaluated using a standardized questionnaire at each study visit. COPD, diabetes mellitus type II, kidney disease and osteoporosis, were assessed at each study visit using spirometry, laboratory testing and dual-energy X-ray absorptiometry, respectively.
**In the comorbidity count analysis all different kinds of comorbidities are summed, in which histological distinct malignancies count as separate events. When participants developed a second (ischemic and haemorrhagic) stroke during the study period this event added extra to the count. A myocardial infarction only counted at the study-visit when it occurred < 24 months prior to that particular study-visit, an second MI could occur again and then added to the count of that particular study visit.
***In the comorbidity DALY analysis, all recurrent events of the same type during the study period added to the DALY equation.
[+]When comorbidities were present before enrolment, we started calculating DALYs 24 months prior to the date of enrolment. For all comorbidities known to be chronic or cause chronic disability (congestive heart failure, angina pectoris, peripheral arterial disease and (ischemic) stroke the duration was estimated from date of diagnosis, until the end of follow-up or end of comorbidity. For all comorbidities assessed at a study visit the duration started one year before the study visit and stopped one year before the next study visit if the disease is then absent. For MI, the duration of the disease was the same as mentioned in the sequela of the MI. For malignancies the time of the disease was set on 5 years, and for osteoporotic fractures the time was set at 12 weeks.
[++]Disability weight with their 95% confidence interval.

Supplementary Table S2: Comorbidities present in participants from the AGE$_h$IV cohort at enrolment (2010-2012) stratified by HIV-status, Amsterdam, the Netherlands

Comorbidities at enrolment (*n*/*N*)	HIV status		p-value*
	HIV-positive	HIV-negative	
Non-AIDS malignancy	9/596 (1·5%)	7/550 (1·3%)	0·73
Congestive heart failure	6/596 (1·0%)	6/550 (1·1%)	0·89
Myocardial infarction	6/596 (1·0%)	0/550 (0·0%)	0·032
Angina pectoris	22/596 (3·7%)	14/550 (2·6%)	0·27
Peripheral arterial disease	13/596 (2·2%)	3/550 (0·6%)	0·022
Ischemic and hemorrhagic stroke	2/596 (0·3%)	2/550 (0·4%)	0·99
Chronic Obstructive Pulmonary Disease	62/596 (10·4%)	45/550 (8·2%)	0·20
Diabetes Mellitus type II	36/595 (6·1%)	25/550 (4·6%)	0·26
Kidney disease	153/596 (25·7%)	39/550 (7·1%)	<0·0001
Osteoporosis	76/575 (13·2%)	34/507 (6·7%)	0·0004

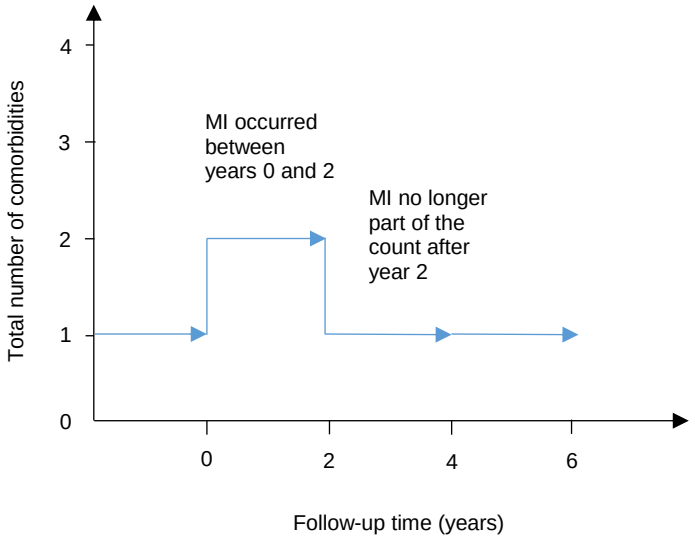
Period prevalence of comorbidities diagnosed during the 24 months prior to enrolment in HIV-positive and HIV-negative participants.

*Period prevalence at enrolment was compared between HIV-positive and HIV-negative participants using a Pearson's χ^2 or Fisher Exact test, where appropriate.

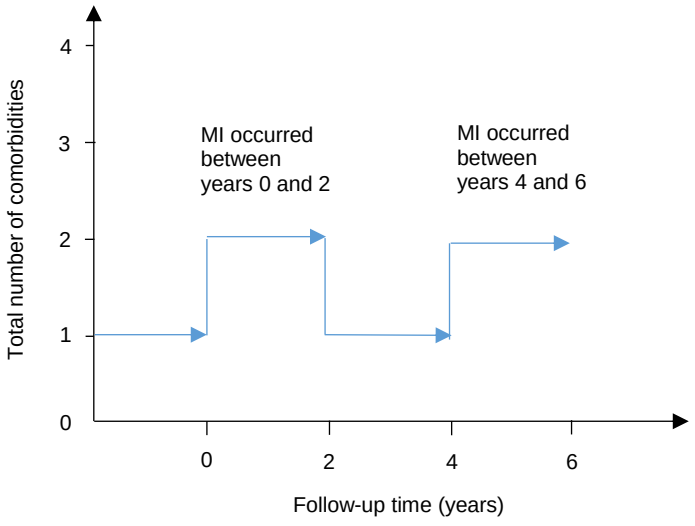
SUPPLEMENTARY FIGURES

Supplementary Figure S1. Examples on how the total number of prevalent comorbidities were handled over time

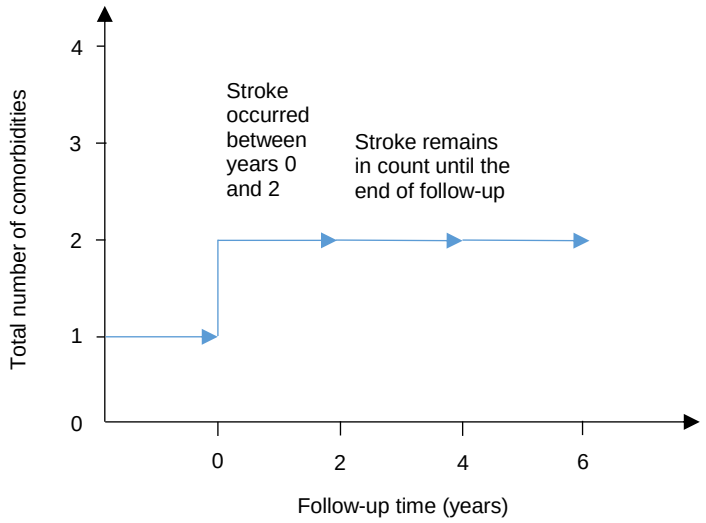
a) Individual with one comorbidity at baseline, only developed MI (and no other comorbidities) during follow-up



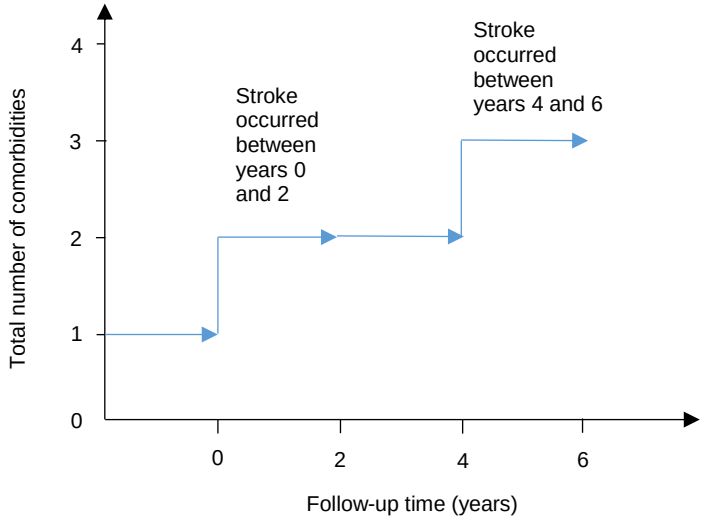
b) Individual with one comorbidity at baseline, developed two MIs (and no other comorbidities) during follow-up



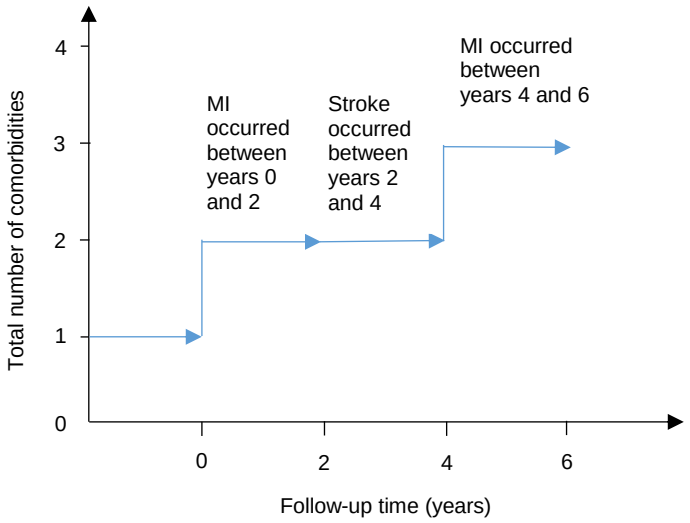
c) Individual with one comorbidity at baseline, only developed stroke (and no other comorbidities) during follow-up



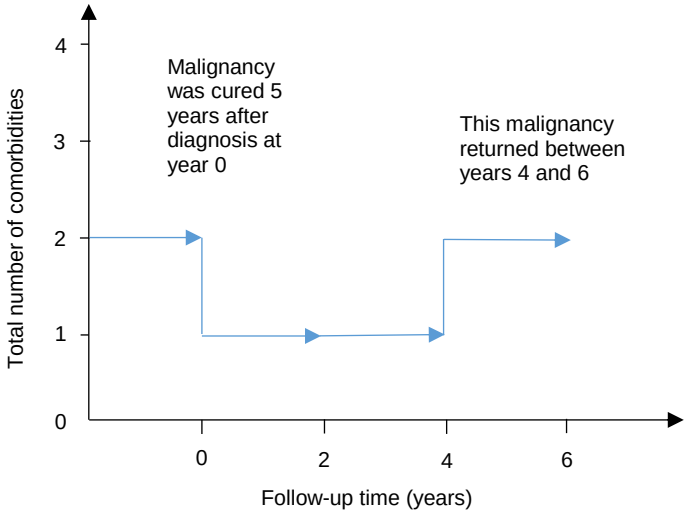
d) Individual with one comorbidity at baseline, developed two strokes (and no other comorbidities) during follow-up



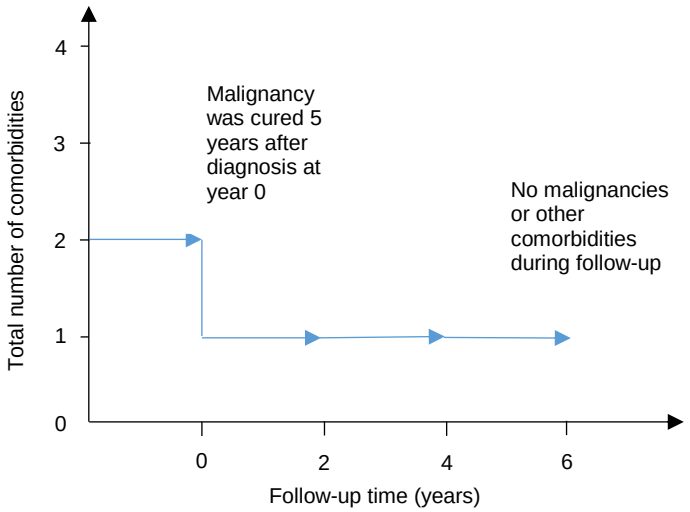
e) Individual with one comorbidity at baseline, developed one stroke and two MIs (and no other comorbidities) during follow-up



f) Individual with two comorbidities at baseline, had remission of one of these comorbidities during follow-up, and remission was temporary (i.e., comes back at a later visit during follow-up)

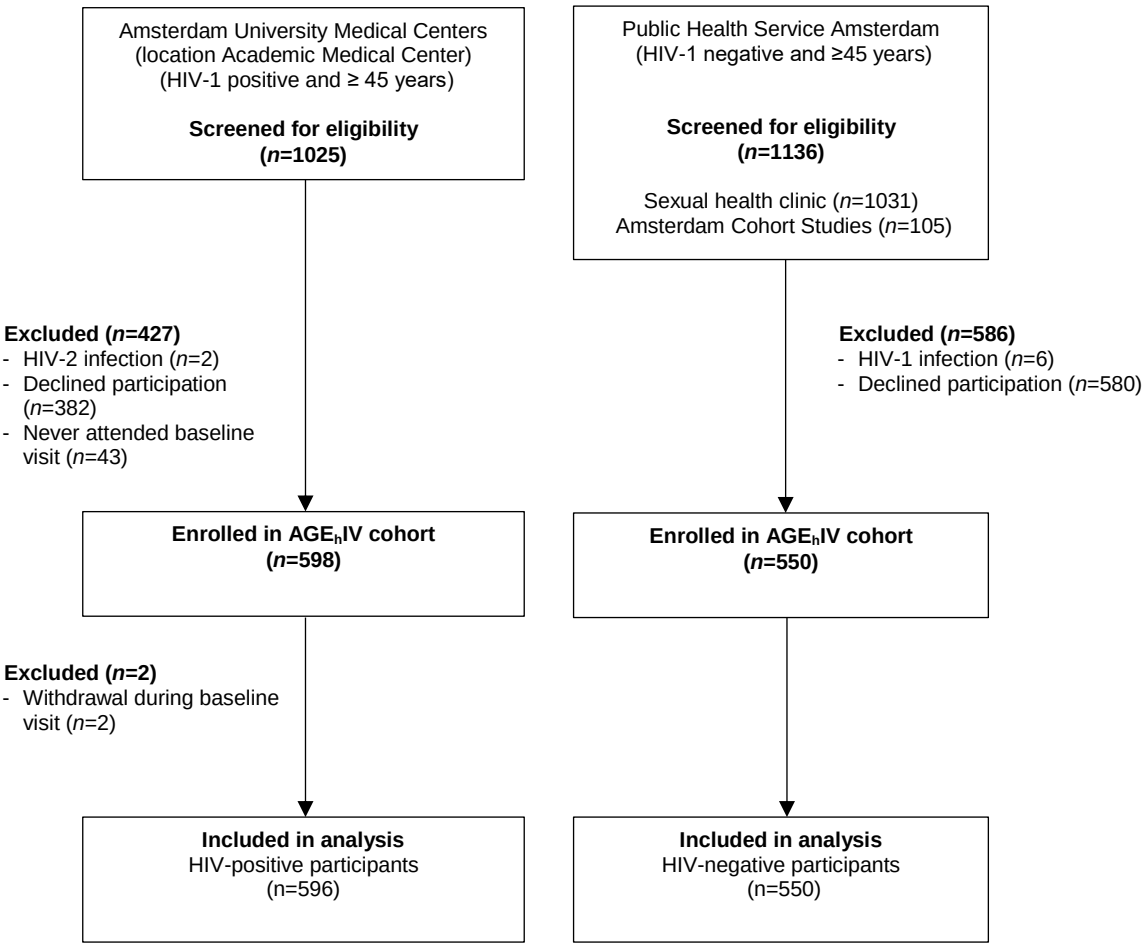


g) Individual with two comorbidities at baseline, had remission of one of these comorbidities during follow-up, and remission was permanent (i.e., no recurrence at a later visit during follow-up)



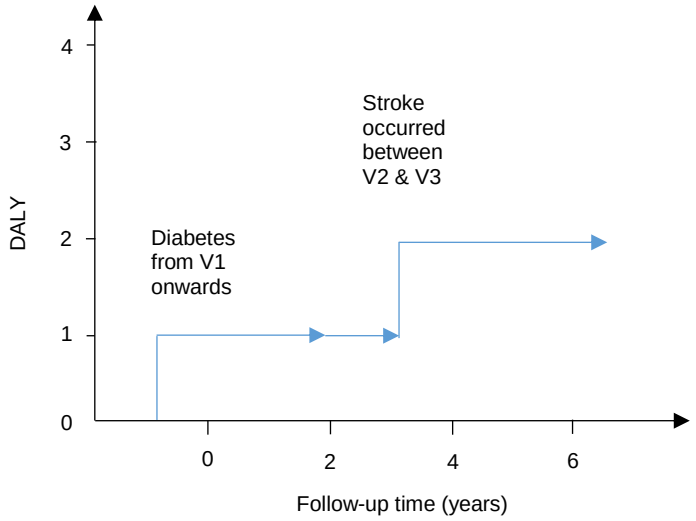
At each follow-up time point, the total number of prevalent comorbidities indicates those comorbidities that occurred within the past 24 months.
Abbreviations: MI, myocardial infarction

Supplementary Figure S2: Flow chart of AGEhIV cohort participants



Supplementary Figure S3. Example of DALY calculation for an individual still alive at end of follow-up (A) or a deceased individual (B)

A



DALY = YLD (duration * DW) + YLL

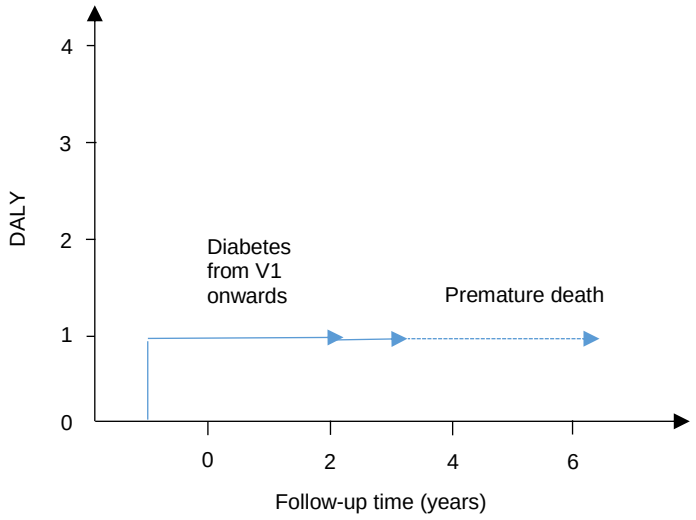
DALY calculation at year 0
Diabetes: 1 yr * 0·049 + 0 = 0·049

DALY calculation at year 2
Diabetes: 2 yrs * 0·049 + 0 = 0·098

DALY calculation at year 4
Diabetes and stroke: 1 yr * 0·049 + 1 yr * (1-(1-0·049)*(1-0·019)) + 0 = 0·116

DALY calculation at year 6
Diabetes and stroke: 2 yr * (1-(1-0·049)*(1-0·019)) = 0·134

B



DALY = YLD (duration * DW) + YLL

DALY calculation at study year 0
Diabetes: 1 yr * 0·049 + 0 = 0·049

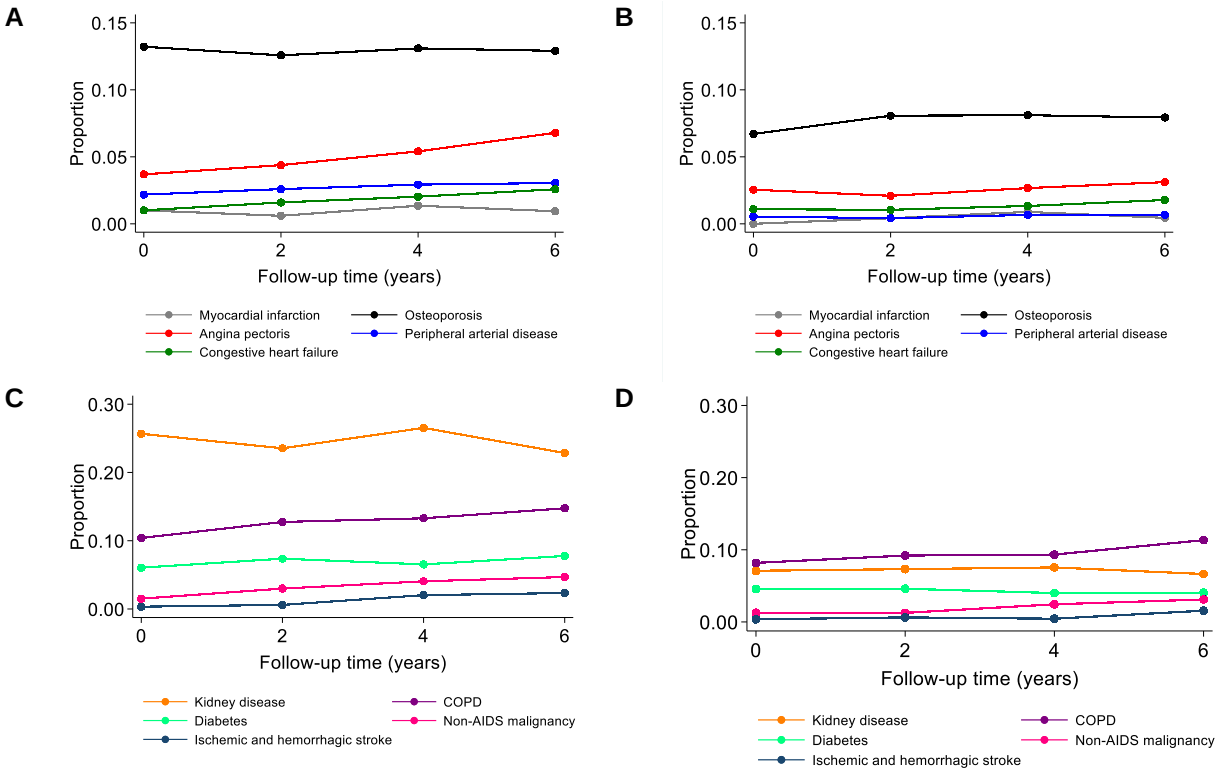
DALY calculation at study year 2
Diabetes: 2 yrs * 0·049 + 0 = 0·098

DALY calculation at study year 4
Diabetes: 1 yr * 0·049 + 1 = 1·049

DALY calculation at study year 6
0 + 2 = 2·0

Abbreviations: DALY, Disability-Adjusted Life Year; YLD, Years Lost due to Disability; DW, Disability Weight. YLL; Years of Life Lost. The disability weights are derived from the Global Burden of Disease Study 2015.

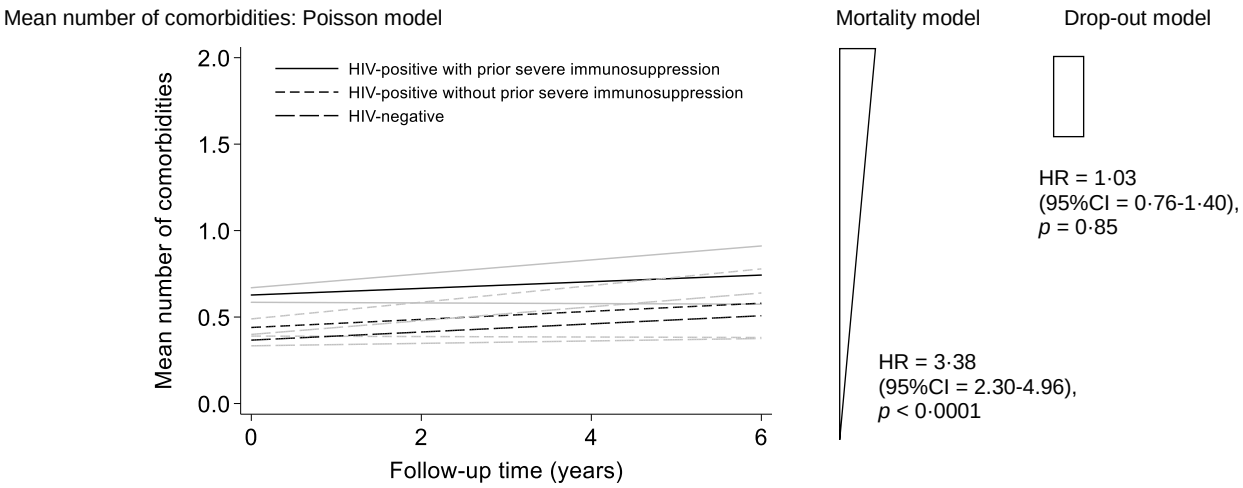
Supplementary Figure S4: Comorbidities observed during the study period, stratified by HIV-status, among participants of the AGEhIV cohort, Amsterdam, the Netherlands, 2010-2018



Period prevalence of comorbidities diagnosed during the 24 months prior to each study visit in people with HIV (PWH) and HIV-negatives. Prevalence of myocardial infarction, osteoporosis, angina pectoris, peripheral arterial disease, and congestive heart failure in PWH (**A**) and HIV-negatives (**B**). Prevalence of kidney disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus type II, non-AIDS malignancy, and ischemic or haemorrhagic stroke in PWH (**C**) and in HIV-negatives (**D**).

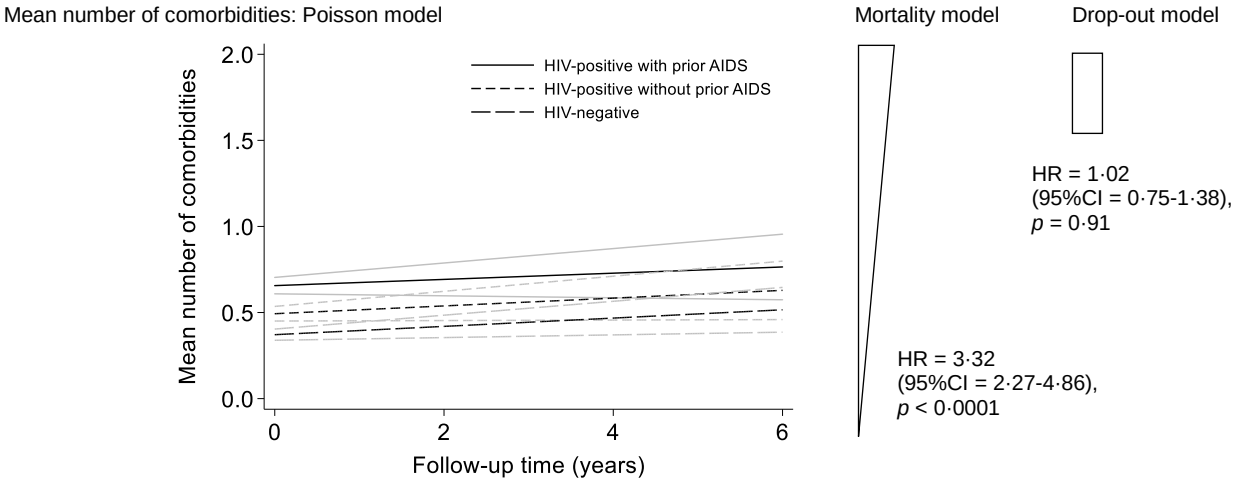
Supplementary Figure S5. Mean number of comorbidities over time; results from the sensitivity analysis in which PWH are stratified by those with and without prior severe immunosuppression (A), with and without prior AIDS (B), with and without prior use of toxic NRTIs (C) among participants of the AGE$_h$IV cohort, Amsterdam, the Netherlands, 2010-2018

A



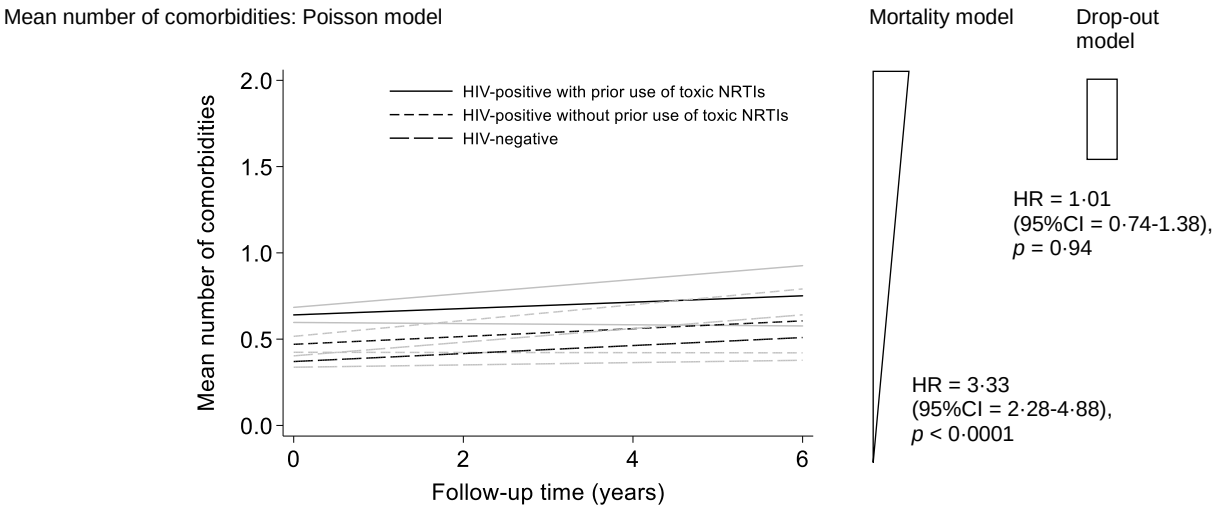
Number in active follow-up				
HIV+ severe	336	279	232	226
HIV+ non-severe	260	220	205	194
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ severe	0	10	20	27
HIV+ non-severe	0	2	3	4
HIV-	0	2	5	7

B



Number in active follow-up				
HIV+ prior AIDS	192	157	133	134
HIV+ no prior AIDS	404	342	304	286
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ prior AIDS	0	9	14	16
HIV+ no prior AIDS	0	3	9	15
HIV-	0	2	5	7

C



Number in active follow-up				
HIV+ toxic NRTIs	270	229	196	191
HIV+ no toxic NRTIs	326	270	241	229
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ prior AIDS	0	6	15	20
HIV+ no prior AIDS	0	6	8	11
HIV-	0	2	5	7

Mean number of comorbidities developed per year of follow-up in participants; results from the joint model while adjusting for age at inclusion, mortality and informative drop-out during the observation period. The solid and dashed black lines represents the mean outcome, with the solid and dashed gray lines representing the 95% confidence intervals. Hazard ratio for mortality shown here per one unit increase of the comorbidity model. The solid black line represents the mean outcome, with the gray lines representing the 95% confidence interval.

In panel (**A**), annual increases in mean number of comorbidities over time were not statistically different between those HIV-positive individuals with and without prior severe immunosuppression (RR per year=1·04, 95%CI=1·00-1·08 and RR per year=1·05, 95%CI=1·00-1·10, respectively) when compared to HIV-negative participants (RR per year=1·05, 95%CI=1·01-1·08) (p for interaction=0·69 and 0·99, respectively).

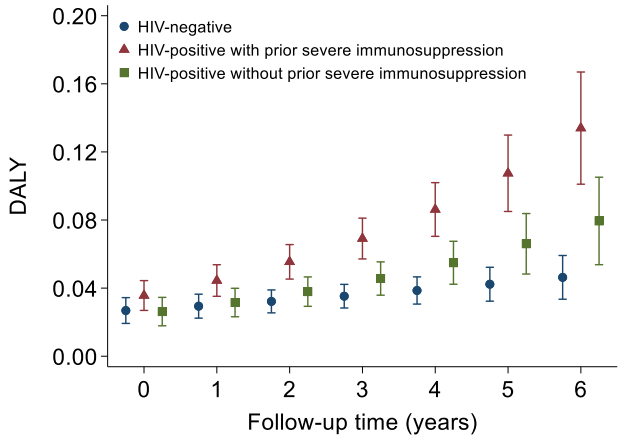
In panel (**B**), annual increases in mean number of comorbidities over time were not statistically different between those HIV-positive individuals with and without prior AIDS (RR per year=1·04, 95%CI=0·99-1·09 and RR per year=1·05, 95%CI=1·00-1·09, respectively) when compared to HIV-negative participants (RR per year=1·05, 95%CI=1·01-1·08) (p for interaction=0·62 and 0·89, respectively).

In panel (**C**), annual increases in mean number of comorbidities over time were not statistically different between those HIV-positive individuals with and without prior use of toxic NRTIs (RR per year=1·04, 95%CI=0·99-1·08 and RR per year=1·05, 95%CI=1·00-1·10, respectively) when compared to HIV-negative participants (RR per year=1·05, 95%CI=1·01-1·08) (p for interaction=0·67 and 0·96, respectively).

Abbreviations: PWH, people with HIV; NRTI, nucleoside-analogue reverse transcriptase inhibitors

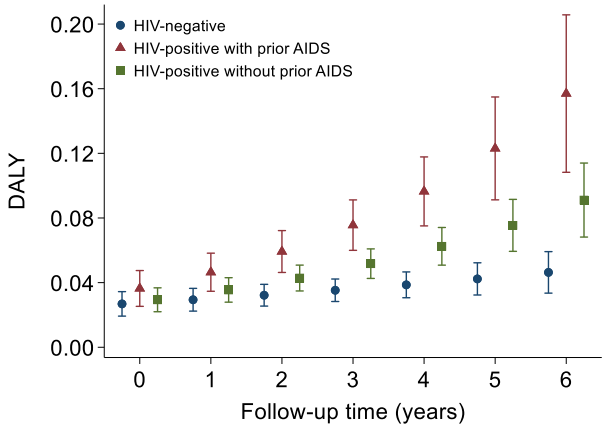
Supplementary Figure S6. Mean DALY development over time; results from the sensitivity analysis in which PWH are stratified in those with and without prior severe immunosuppression (A), with and without prior AIDS (B), or with and without prior use of toxic NRTI (C) among participants of the AGE$_h$IV cohort, Amsterdam, the Netherlands, 2010-2018

A



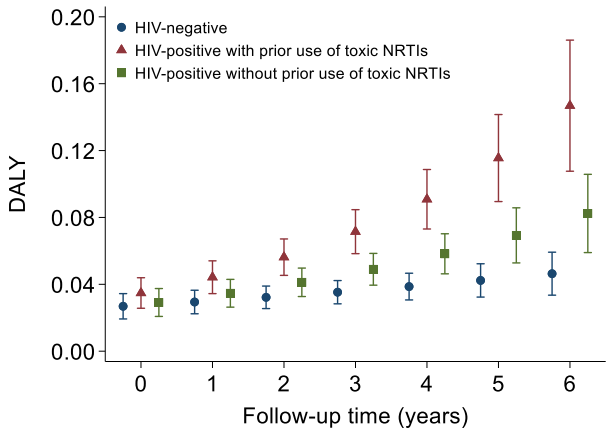
Number in active follow-up				
HIV+ severe	336	279	232	226
HIV+ non-severe	260	220	205	194
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ severe	0	10	20	27
HIV+ non-severe	0	2	3	4
HIV-	0	2	5	7

B



Number in active follow-up				
HIV+ prior AIDS	192	157	133	134
HIV+ no prior AIDS	404	342	304	286
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ prior AIDS	0	9	14	16
HIV+ no prior AIDS	0	3	9	15
HIV-	0	2	5	7

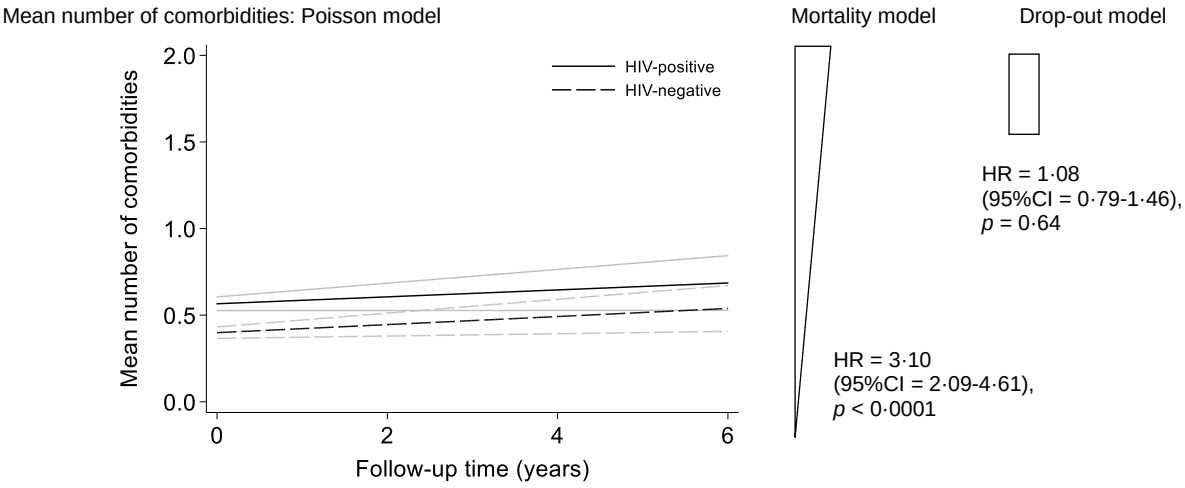
C



Number in active follow-up				
HIV+ toxic NRTIs	270	229	196	191
HIV+ no toxic NRTIs	326	270	241	229
HIV-	550	481	457	457
Number deceased, cumulative				
HIV+ prior AIDS	0	6	15	20
HIV+ no prior AIDS	0	6	8	11
HIV-	0	2	5	7

In the figures, the mean estimates with their 95% confidence interval, as obtained from the hurdle model, are shown.
Abbreviations: AIDS, acquired immunodeficiency disorder; DALY, Disability-Adjusted Life Year; PWH, people with HIV; NRTI, nucleoside-analogue reverse transcriptase inhibitors.

Supplementary Figure S7. Modelled mean number of comorbidities over time at enrolment among participants of the AGE$_h$IV cohort; results from joint model with random intercept while additionally adjusting for current smoking and alcohol use* in the Poisson submodel, Amsterdam, the Netherlands, 2010-2018



Number in active follow-up				
HIV-positive	596	499	437	420
HIV-negative	550	481	457	457
Number deceased, cumulative				
HIV-positive	0	12	23	31
HIV-negative	0	2	5	7

Results from the joint model while adjusting for mortality and informative drop-out during the observation period. The solid and dashed black lines represents the mean outcome, with the solid and dashed gray lines representing the 95% confidence intervals. Hazard ratios for mortality and drop-out shown here per one unit increase of the comorbidity model.

Increases in mean number of comorbidities observed in HIV-positive and HIV-negative participants were not statistically different (RR 1·04, 95%CI=1·00-1·08 and 1·05, 95%CI=1·01-1·08, respectively; p for interaction=0·74).

*Alcohol use defined as drinking > 5 (for men) or >4 (for women) units of alcohol daily or almost daily.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

SUPPLEMENTARY REFERENCES

1. Amsterdam Cohort Studies. Available at: https://www.cohortstudies.nl/. Accessed 13 October 2022.
2. HIV Monitoring Foundation. Available at: http://www.hiv-monitoring.nl/en. Accessed 13 October 2022.
3. Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M, et al. Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res. 2002;17(12):2237-46.
4. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2015 (GBD 2015) Reference Life Table. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016. Available at: https://ghdx.healthdata.org/record/ihme-data/gbd-2015-reference-life-table. Accessed 13 October 2022.
5. Hilderink HB, Plasmans MH, Snijders BE, Boshuizen HC, Poos MJ, van Gool CH. Accounting for multimorbidity can affect the estimation of the Burden of Disease: a comparison of approaches. Arch Public Health. 2016;74:37.