Age-associated dementia among older people aging with HIV in the United States: a modeling study

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Objective: Almost 400 000 people with HIV (PWH) in the United States are over age 55 years and at risk for age-associated dementias (AAD), including Alzheimer's disease and vascular contributions to cognitive impairment and dementia (VCID). We projected the cumulative incidence and mortality associated with AAD among PWH at least 60 years in the United States compared with the general population.

Design/methods: Integrating the CEPAC and AgeD-Pol models, we simulated two cohorts of 60-year-old male and female individuals: PWH, and the general US population. We estimated AAD incidence and AAD-associated mortality rates. Projected outcomes included AAD cumulative incidence, life expectancy, and quality-adjusted life-years (QALYs). We performed sensitivity and scenario analyses on AAD-specific (e.g. incidence) and HIV-specific (e.g. disengagement from HIV care) parameters, as well as premature aging among PWH.

Results: We projected that 22.1%/16.3% of 60-year-old male individuals/female individuals with HIV would develop AAD by 80 years compared with 15.9%/13.3% of male individuals/female individuals in the general population. Accounting for age-associated and dementia-associated quality of life, 60-year-old PWH would have a lower life expectancy (QALYs): 17.4 years (14.1 QALYs) and 16.8 years (13.4 QALYs) for male and female individuals, respectively, compared with the general population [male individuals, 21.7 years (18.4 QALYs); female individuals, 24.7 years (20.2 QALYs)]. AAD cumulative incidence was most sensitive to non-HIV-related mortality, engagement in HIV care, and AAD incidence rates.

Conclusion: Projected estimates of AAD-associated morbidity, mortality, and quality of life can inform decision-makers and health systems planning as the population of PWH ages. Improved AAD prevention, treatment, and supportive care planning are critical for people aging with HIV.

AIDS 2024, **38**:1186–1197

Keywords: aging, cognitive impairment, comorbidity, dementia, HIV, simulation modeling

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Received: 31 August 2023; revised: 29 December 2023; accepted: 1 February 2024.

DOI:10.1097/QAD.0000000000003862

ISSN 0269-9370

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Introduction

With antiretroviral therapy (ART), people with HIV (PWH) are aging and expected to attain life expectancies near those of the general population [1]. In 2019, almost 400 000 (38%) people living with diagnosed HIV in the United States were 55 years or older [2]. Older PWH are at increased risk for comorbidities, such as cardiovascular disease and dementia, which can be either accentuated or accelerated because of HIV [3–6].

Age-associated dementias (AAD), such as Alzheimer's disease and vascular contributions to cognitive impairment and dementia (VCID), are increasingly common in the general US population. With more people aging into their 80s, the burden of AAD in the United States is projected to more than double from 5.8 million in 2019 to 13.9 million by 2060 [7–9]. AAD has been rarely reported among PWH because of historical challenges with distinguishing AAD from HIV-associated neurocognitive disorder (HAND); additionally, most PWH are only recently reaching ages at which AAD is diagnosed [10–12]. AAD is expected to affect PWH when they age beyond 60 years, at least at similar rates as in the general population, if not more frequently [6,13].

Beyond age as a risk factor, PWH are at increased risk of developing AAD because of pathophysiologic mechanisms, including abnormal deposition of amyloid and other proteins associated with neurodegeneration [14,15], immune activation [16,17], vascular diseases [18,19], and brain atrophy [12]. Additionally, compared with the general population, PWH are at increased risk for VCID because of higher rates of smoking [20,21], as well as higher risks of diabetes, hypertension, atherosclerosis, and stroke [22,23]. Recent data suggest that AAD incidence among PWH may be almost twice that of people without HIV within the same healthcare system [6].

As the population of PWH in the United States ages, evidence-based projections of AAD-associated morbidity, quality of life, and mortality are essential for health services planning, coordination of AAD and HIV care, and expansion of services that are effective and affordable. Our objective was to populate a microsimulation model for HIV and AAD and then simulate cumulative AAD incidence and life expectancy for 60-year-old people with and without HIV in the United States.

Methods

Analytic overview

We expanded the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model of HIV natural history and treatment to incorporate features of the Age-associated Dementia Policy (AgeD-Pol) model, a computer microsimulation model that projects age-specific and sex-specific prevalence, incidence, and mortality of AAD in the United States. We simulated male and female cohorts: people with HIV ('PWH') and the general US population. At model start, all people are 60 years old and without AAD. We parameterized AAD-associated input parameters (i.e. AAD incidence, progression, and mortality) with data from the general US population; for AAD incidence in PWH, we increased age-stratified/sex-stratified AAD incidence as recently reported [6]. We accounted for competing risks of deaths from HIV-related and non-HIV/non-AAD-related causes. We projected the 10-year, 20-year, and lifetime cumulative AAD incidence, as well as overall life expectancy, and quality-adjusted life-years for PWH and the general US population.

Model structure

The age-associated dementia policy (AgeD-pol) model

The AgeD-Pol model is a microsimulation model of age-associated dementia previously validated for the general US population [24,25]. Simulated individuals are assigned AAD status at model start based on age-stratified and sex-stratified AAD prevalence. As individuals without AAD progress throughout the simulation, they are subject to age-stratified/sex-stratified monthly AAD incidence. Individuals with AAD can progress from mild to moderate disease to severe disease; prior studies have suggested that only individuals with severe AAD experience AAD-associated mortality [26–28]. Therefore, only simulated people with severe AAD incur an additional risk for monthly AAD-related mortality, in addition to non-AAD-related mortality.

The Cost-Effectiveness of Preventing AIDS Complications model

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model is a validated microsimulation of HIV disease and treatment [29–32]. Upon entry into the model, simulated individuals draw for $CD4^+$ count and HIV RNA from user-defined initial distributions. Simulated PWH in care are treated with ART and transition monthly between health states defined by $CD4^+$ count, HIV RNA, history of opportunistic infection, and ART use. They can disengage from HIV care, stop ART, and subsequently return to care and reinitiate ART. Death among PWH can occur from HIV-related causes (opportunistic infection or chronic HIV-related mortality), AAD, or other non-HIV-related/non-AAD-related causes (e.g. cancers, suicide). Model details are available at https://www.massgeneral.org/medicine/mpec/research/cpac-model.

Simulated cohorts

We simulated male and female cohorts of PWH and the general US population who are 60 years old at model start. Compared with the general US population, PWH are at risk for HIV-related mortality and at increased risk of age-stratified and sex-stratified

non-HIV-related/non-AAD-related mortality that reflects the proportions of PWH from different HIV acquisition risk groups defined by the Centers for Disease Control and Prevention (CDC): men who have sex with men (MSM); people who ever used injection drugs (PWID); people who are heterosexually active at increased risk for HIV acquisition [31,33,34]. The general US population consists of people without HIV who experience average non-HIV-related/non-AAD-related mortality.

Input parameters

Cohort characteristics

We assigned cohort characteristics (e.g. age, sex at birth, $CD4^+$ count) to simulated PWH at model start based on whether they are on ART (75% of PWH; mean $CD4^+$ 600 cells/μl) or disengaged from HIV care and not taking ART (25% of PWH; mean $CD4^+$ 325 cells/μl) [35,36]; 71–73% of all PWH are virologically suppressed (80% of PWH in care) [37–39]. During the simulation, PWH experience monthly rates of disengagement from care and stopping ART (0.01–15%/month depending on adherence), and returning to care with ART reinitiation (3%/month after 12 months of loss to follow-up) [2,40] (Table 1).

Age-associated dementia incidence

For the general population, we derived age-stratified/sex-stratified AAD incidence rates from the Adult Changes in Thought (ACT) study, a prospective cohort study of dementia among the general population in Seattle, WA, that uses prospective screening with adjudication of new dementia diagnoses by a multidisciplinary team [41]. We estimated that AAD monthly incidence rates were 1.8 times higher for PWH compared with the general US population [6].

Quality of life

To incorporate health utilities that account for age-associated and dementia-associated QoL for the general population and PWH, we defined a sex-stratified baseline QoL. Then, we incorporated reductions in QoL because of age (in 5-year increments) and dementia. We stratified dementia QoL by disease stage (i.e. mild, moderate, and severe AAD), using marginal disutility values from the regression results of EQ-5D values taken from the Medical Expenditure Panel Survey, which are already adjusted for age, sex at birth, race/ethnicity, comorbidity, education, and income [42]. PWH experience an additional QoL decrement from chronic HIV and acute opportunistic infections (−0.036) [42].

Mortality

Three distinct sources of mortality are incorporated into the model: AAD-related (for people with AAD regardless of HIV status), non-HIV-related/non-AAD-related (for all people), HIV-related (for PWH only). We derived age-stratified/sex-stratified AAD-associated and non-AAD-associated mortality from the Human Mortality Database 2019 and the Multiple Cause-of-Death Mortality Data from the National Bureau of Economic Research [43,44], which we applied to the general population and PWH with AAD. We also derived age-stratified/sex-stratified non-HIV-related/non-AAD-related mortality for the general population [43,44].

To account for increased non-HIV-related/non-AAD-related mortality among PWH because of substance use, systemic racism, and poverty, among other structural barriers [32,44–46], we developed relative mortality ratios from the National Health and Nutrition Examination Survey (NHANES) to quantify independent associations of mortality with the major HIV acquisition risk categories compared with the general population [47,48]. We applied these relative mortality ratios to the age-stratified/sex-stratified, non-HIV-related/non-AAD-related mortality rates, weighted by the distribution of the major HIV risk acquisition groups among PWH in the United States [2]. Last, PWH also experience additional $CD4^+$-stratified HIV-related mortality, including from opportunistic infections [49].

Sensitivity and scenario analyses

We performed univariate sensitivity analyses on selected input parameters for the PWH cohorts given uncertainty in the natural history of AAD in PWH: AAD incidence, AAD progression rates, AAD-associated mortality, and AAD-associated quality-of-life. We also varied non-HIV-related/non-AAD-related mortality rates among PWH. Then, we examined scenarios of improved HIV clinical care: no disengagement from care (i.e. all start in care with standard rates of virologic suppression and no loss to follow-up) and 100% sustained virologic suppression among all PWH in care (i.e. perfect virologic suppression with standard rates of loss to follow-up). Each scenario decreases HIV-related mortality by increasing $CD4^+$ counts. We also assessed the potential impact of 'premature aging' on PWH by incorporating an age-stratified forward shift in AAD incidence and non-HIV-related/non-AAD-related mortality by 5 years (i.e. model inputs for AAD incidence and non-HIV-related/non-AAD-related mortality of 70-year-old male individuals were instead applied to 65-year-old male individuals) [50,51]. Last, we performed multivariate sensitivity analysis on the most influential parameters by varying simultaneously: 1) age-stratified AAD incidence rates and monthly probability of disengagement from HIV care, and 2) age-stratified AAD incidence rates and non-HIV-related mortality rates among PWH.

Results

Base case

For 60-year-old male individuals, model-projected cumulative incidence of AAD would be 8.7%/22.1%/34.1% and 5.3%/15.9%/34.1% at 70 years, 80 years, and lifetime among PWH and in the general population, respectively (Table 2 and Fig. 1a). We projected a

Table 1. Input parameters for analysis of age-associated dementia risk in people aged 60 years and older in the United States.

Input parameter	Base case value				
Cohort characteristics	All cohorts		Sensitivity analysis range		Reference
Age, mean (years)	60				
Initial $CD4^+$ cell count (cells/μl) (SD)					
Diagnosed, on ART	600 (313)				[35]
Diagnosed, not in care	325 (53)				[36] [a]
Virologic suppression among PWH in care (%)	80				[37–39] [a]
Monthly probability of disengagement from care, range by adherence (%)	0.01–15		100		[2,40] [a]
Monthly probability of return to care (%)	3.0				Assumption
Proportion of population with HIV (%)	Male individuals	Female individuals			
MSM	79.9	–			
People who have ever injected drugs	9.2	20.6			[2]
Heterosexually active individuals at increased risk for HIV	10.9	79.4			
AAD-related inputs					
General population AAD incidence, per 1000 person-years					
Age, years, mean (SD)	Male individuals	Female individuals			
60–64	4.5[b]	3.2[b]			[72,73] [a]
65–69	7.4	3.8			
70–74	11.4	7.9			
75–79	21.1	18.1			[41] [a]
80–84	49.2	44.7			
85+	80.8[c]	94.1[c]			[6]
AAD incidence rate ratio: PWH vs. general population	1.8	1.8	1.4–2.2		
Duration of AAD stages, months (SD)			0.5–2×		
Mild to moderate AAD	43.6 (37.0)				[74,75] [a]
Moderate to severe AAD	24.0 (16.7)				
AAD-associated quality of life decrement by stage			0.75–1.25×		
Mild	−0.09				
Moderate	−0.18				[42] [a]
Severe	−0.26				
Mortality					
Monthly AAD-associated mortality among people with severe AAD, %			0.5–2.0×		
Age (years)	Male individuals	Female individuals			
60–64	0.002	0.001			
65–69	0.004	0.004			
70–74	0.013	0.011			
75–79	0.036	0.034			[27,44] [a]
80–84	0.092	0.093			
85+	0.280	0.350			
Non-HIV, non-AAD-related mortality, monthly (%)	Male individuals	Female individuals			
Ages 60–64 years	0.094–0.125	0.058–0.074			
Ages 65–69 years	0.135–0.166	0.079–0.104			
Ages 70–74 years	0.179–0.241	0.115–0.159			[43,44] [a]
Ages 75–79 years	0.259–0.364	0.172–0.248			
Ages 80–84 years	0.398–0.583	0.269–0.394			
Ages 85+	0.619–2.668	0.423–1.849			
Relative mortality ratios applied to non-HIV-related/non-AAD-related mortality for PWH, mean (95% CI)[a,d]	Male individuals	Female individuals	Male individuals	Female individuals	
MSM	1.5 [1.0–2.3]	–			
People who have ever injected drugs	1.7 [1.1–2.5]	3.5 [2.0–6.0]			[2,34] [a]
Heterosexually active individuals at increased risk for HIV	1.7 [1.0–2.1]	2.4 [1.9–3.0]			
Weighted average	1.5 [1.1–1.9]	2.6 [2.3–3.6]	1.0–4.0	1.0–4.0	
Monthly probability of chronic HIV mortality by $CD4^+$ count (cells/μl), range by OI history (%)					
>500 cells/μl	0.003				
351–500 cells/μl	0.011				
201–350 cells/μl	0.021				
101–200 cells/μl	0.020–0.270				[43,53,76–80] [a]
50–100 cells/μl	0.028–0.270				
<50 cells/μl	0.120–0.560				

AAD, age-associated dementia; ART, antiretroviral therapy; DTG, dolutegravir; MSM, men who have sex with mex; OI, opportunistic infection; PI, protease inhibitor; PWH, people with diagnosed HIV; SD, standard deviation.
[a]Inputs derived from listed sources.
[b]The AAD incidence rate for ages 60–64 years was derived from estimates reported by Knopman *et al.* 2005 and the World Alzheimer's Report 2015 [37,38].
[c]The AAD incidence rate for ages 85+ is an average of the 80–84 and 85+ age groups reported by Tom *et al.* 2015 [36].
[d]Relative mortality ratios compare people in each risk group with the general population.

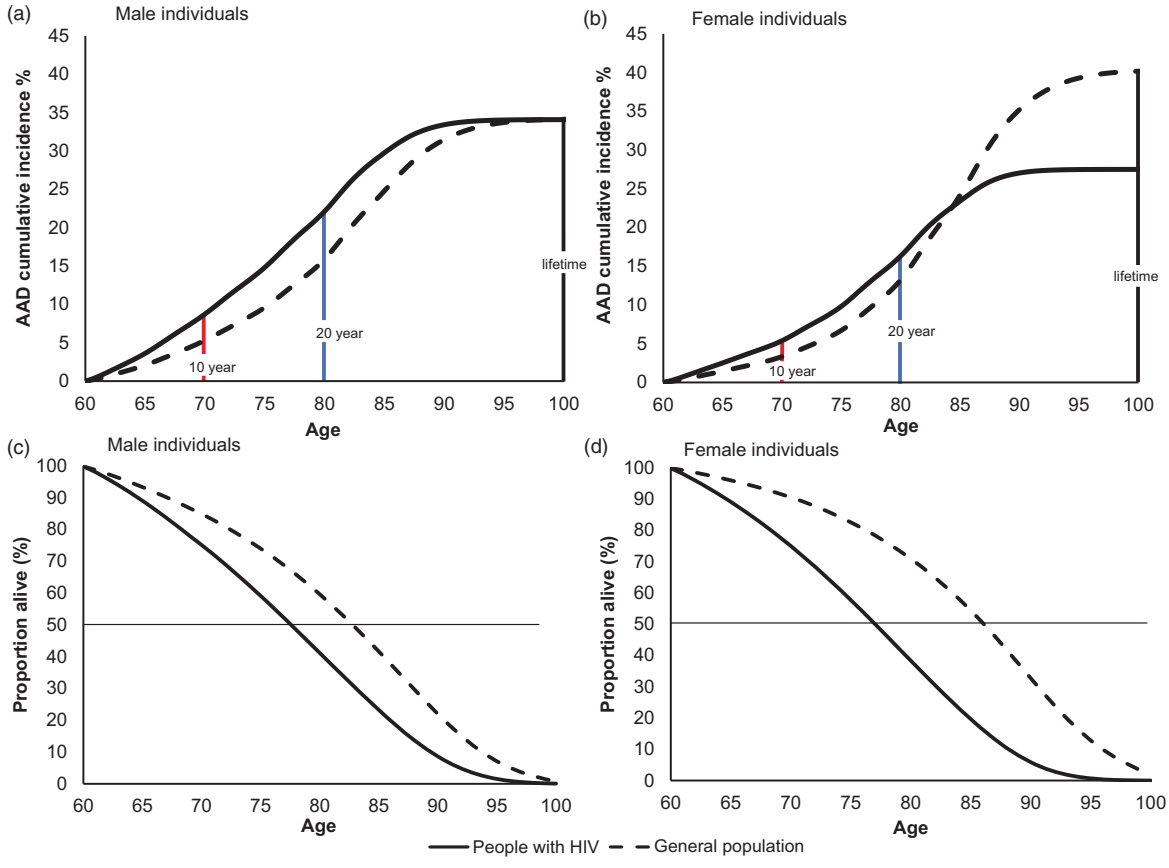

Fig. 1. Model-projected lifetime age-associated dementia cumulative incidence and survival among 60-year-old male and female individuals in the United States: comparing people with HIV and people in the general US population. The model-projected lifetime AAD cumulative incidence is displayed for male individuals (panel a), and female individuals (panel b); the vertical lines show the AAD cumulative incidence at 10 years (red), 20 years (blue), and lifetime (black). Model-projected survival is shown for male individuals (panel c) and female individuals (panel d). The solid lines represent people with HIV, and the dashed lines represent the general US population. AAD, age-associated dementia.

cumulative incidence of AAD for 60-year-old female individuals of 5.4%/16.3%/27.5% and 3.3%/13.3%/40.2% at 70 years, 80 years, and lifetime among PWH and in the general population (Table 2 and Fig. 1b).

We projected life expectancy (unadjusted years) and quality-adjusted life years (QALYs) for 60-year-old male individuals with HIV to be 17.4 years (14.1 QALYs) compared with 21.7 years (18.4 QALYs) among male individuals, from the general US population (Table 2 and Fig. 1c). Among 60-year-old female individuals with HIV, we projected 16.8 years of life (13.4 QALYs) compared with 24.7 years (20.2 QALYs) among female individuals from the general US population (Table 2 and Fig. 1d). These model-based estimates for life expectancy in the general population are consistent with published data [52].

Sensitivity and scenario analyses

Age-associated dementia-associated parameters

Lifetime AAD cumulative incidence was substantially influenced by the estimated age-stratified/sex-stratified AAD incidence rates among PWH. Applying the lower bound AAD incidence rate ratio (IRR) (1.6×) or upper bound AAD IRR (2.0×) for PWH compared with the base case would result in a range of lifetime AAD cumulative incidence (male individuals: 31.7–36.3 versus 34.1%; female individuals: 25.4–29.4 versus 27.5%) (Table 2 and Fig. 2a and 2b, yellow and orange squares). For male individuals with HIV, lifetime AAD cumulative incidence would be higher than among male individuals in the general population when applying the upper bound AAD IRR. However, lifetime AAD cumulative incidence remained lower among female individuals with HIV than female individuals in the general population, even at the highest estimated AAD incidence rates among PWH, given the greater risks of competing mortality among female individuals with HIV (Fig. 2d, yellow square). A range of values in other AAD-focused parameters had minimal influence on projected outcomes (Table 2).

Non-HIV-related/non-AAD-related mortality

Estimated non-HIV-related/non-AAD-related mortality also had a major impact on AAD cumulative incidence. With lower non-HIV-related/non-AAD-related mortality

Table 2. Base case, sensitivity, and scenario analysis in a modeling analysis of age-associated dementia among people with HIV in the United States: projected life years, quality-adjusted life years, age-associated dementia cumulative incidence (10-year, 20-year, and lifetime).

	AAD cumulative incidence at 70 years (%)		AAD cumulative incidence at 80 years (%)		Lifetime AAD cumulative incidence (%)		Life years		Quality-adjusted life years	
Population	Male individuals	Female individuals	Male individuals	Female individuals	Male individuals	Female individuals	Male individuals	Female individuals	Male individuals	Female individuals
Base case										
PWH	8.7	5.4	22.1	16.3	34.1	27.5	17.4	16.8	14.1	13.4
General	5.3	3.3	15.9	13.3	34.1	40.2	21.7	24.7	18.4	20.2
Varying AAD in PWH										
Lower AAD incidence rate (1.6×)	7.8	4.8	20.0	14.7	31.7	25.4	17.4	16.8	14.1	13.4
Higher AAD incidence rate (2.0×)	9.7	6.0	24.1	18.0	36.3	29.4	17.3	16.8	14.0	13.3
5-years premature aging	13.3	8.6	31.0	24.6	36.1	29.3	14.4	13.7	11.6	10.9
Varying non-HIV-related/non-AAD-related mortality in PWH										
Lower non-HIV-related/non-AAD-related mortality rate (M:1.1×; F:1.9×)	9.1	5.6	24.8	18.1	43.1	34.1	20.2	18.7	16.2	14.8
Higher non-HIV-related/non-AAD-related mortality rate (M: 2.3×; F: 3.6×)	8.3	5.2	18.9	14.4	25.7	21.9	14.6	14.9	12.0	11.9
Varying HIV-related parameters in PWH										
No disengagement from care	8.9	5.5	23.1	17.1	36.3	29.5	18.1	17.5	14.6	13.8
100% virologic suppression among PWH engaged in care	8.8	5.4	22.5	16.7	35.0	28.3	17.6	17.0	14.3	13.6

AAD, age-associated dementia; PWH, people with HIV.

for PWH (Table 1), life expectancy would increase compared with the base case [male individuls: 20.2 years (16.2 QALYs) versus 17.4 years (14.1 QALYs); female individuals: 18.7 years [14.8 QALYs] versus 16.8 years (13.4 QALYs)] (Table 2 and Fig. 2a and b green circle). With lower non-HIV-related/non-AAD-related mortality, AAD cumulative incidence for PWH would increase compared with the base case (male individuals: 43.1 versus 34.1%; female individuals: 34.1 versus 27.5%); despite the increased life expectancy and AAD cumulative incidence, model-based projections for female individuals with HIV would remain lower than for the general population (Table 2 and Fig. 2c and d, green circles). Increasing the rates of non-HIV-related/non-AAD-related mortality among PWH would have the greatest effect on decreasing AAD cumulative incidence, life expectancy, and QALYs compared with the base case (Table 2 and Fig. 2, purple circles).

HIV-related parameters

Improving engagement in care among PWH would result in a higher lifetime cumulative incidence of AAD (male individuals: 36.3 versus 34.1%; female individuals: 29.5 versus 27.5%) given increased life expectancy compared with the base case (Table 2 and Fig. 2, blue diamonds). Eliminating disengagement from HIV care would increase life expectancy and AAD cumulative incidence more than improving virologic suppression to 100% among people already in care (Table 2). Changes to HIV-related parameters resulted in lifetime AAD cumulative incidence among PWH surpassing estimates among the general population for male indivduals but not female individuals.

Premature aging scenario analysis

Simulating premature aging among PWH, we projected greater AAD cumulative incidence and lower life expectancy compared with the base case (Table 2 and Fig. 2a and b, red triangles). Model-projected AAD cumulative incidence at 70 and 80 years of age would be higher among male individuals and female individuals with HIV when accounting for premature aging (male individuals: 70 years, 13.3% and 80 years, 31%; female individuals: 70 years, 8.6% and 80 years, 24.6%) compared with the general population (Table 2 and Fig. 2a and b, red triangles), and life expectancy would remain lower [male individuals: 14.4 (11.6 QALYs); female individuals: 13.7 years (10.9 QALYs)] (Table 2 and Fig. 2c and d, red triangles). When accounting for premature aging, model-projected lifetime AAD cumulative incidence would be higher for PWH than for the general population among male individuals (36.1 versus 34.1%) but would remain lower for PWH than for the general population among female individuals (29.3 versus 40.2%).

Two-way sensitivity analyses

We examined the impact of changes in engagement in HIV care and AAD incidence rates on the lifetime cumulative incidence of AAD among PWH (Fig. 3a). When people are more engaged in HIV care (i.e. lower probability of HIV-related mortality), we projected that lifetime AAD cumulative incidence would rise among PWH, especially as AAD incidence rates increase (bottom and right of Fig. 3a). If disengagement from care was 5% or less over 3 years and AAD incidence rates among PWH were 1.6× the general population, or if disengagement from care was 20% or less at 3 years and AAD incidence rates were greater than 1.8× the general population (Fig. 3a, top left panel), AAD cumulative incidence among male individuals with HIV would surpass the general population. Among female individuals with HIV, lifetime AAD cumulative incidence would be lower than in the general female population even with no disengagement

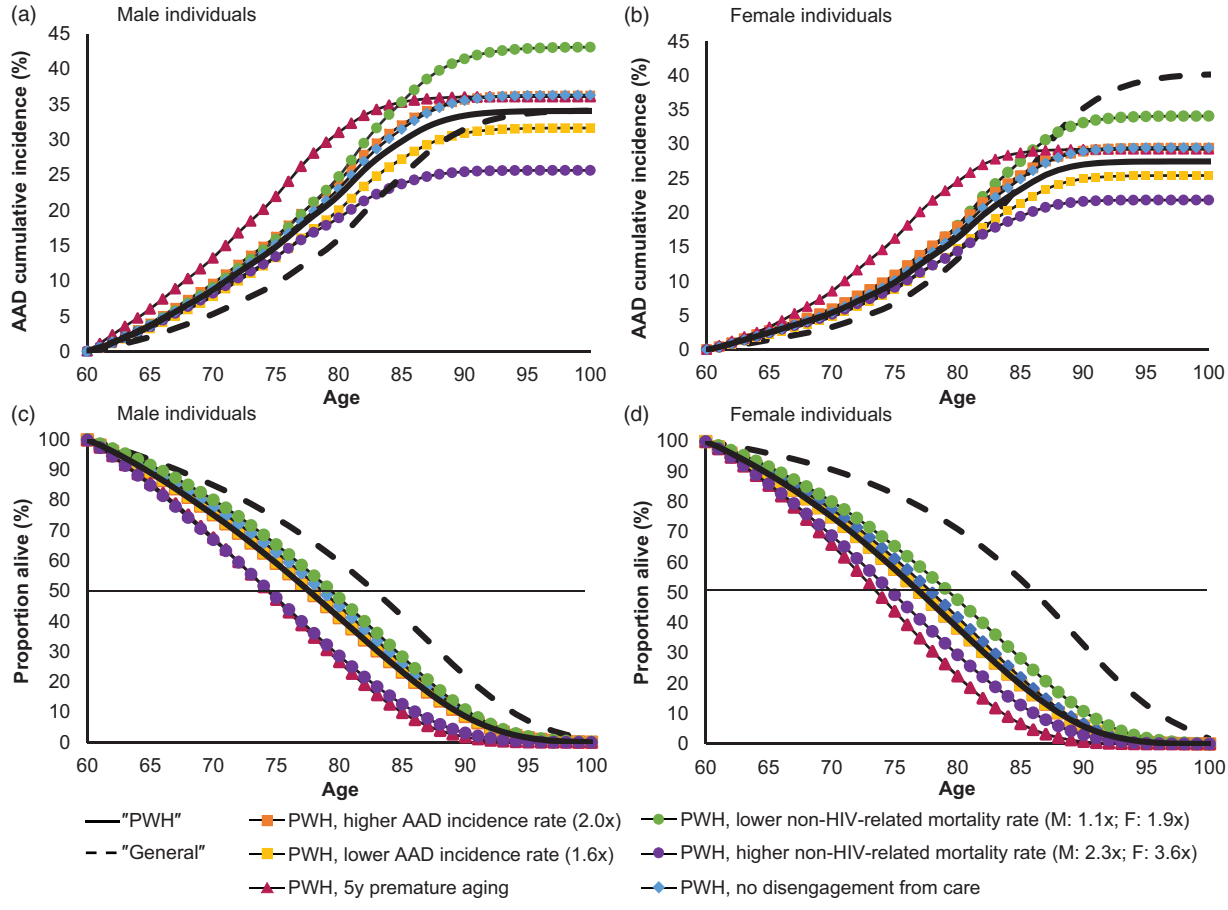

Fig. 2. Effects of varying AAD- and HIV-associated parameters on the lifetime AAD cumulative incidence and survival among male and female individuals with HIV compared with the general US population. This figure shows the results of one-way sensitivity analyses and scenario analyses, varying HIV-associated and AAD-associated parameters on lifetime AAD cumulative incidence and survival. Panels a and b report the lifetime AAD cumulative incidence for male and female individuals; panels c and d report survival outcomes for male and female individuals. The black dashed and solid lines represent the AAD cumulative incidence in the base case for the 'general' and 'PWH' cohorts, respectively. The yellow and orange square lines represent lower and higher AAD cumulative incidence rates when applying the lower (1.6×) and upper bounds (2.0×) of the AAD incidence rate ratio for PWH compared with the general population [6]. The green and purple circle lines represent the cumulative incidence of AAD when the relative mortality ratios were adjusted to the lower and upper bounds of the 95% confidence intervals (male individuals, 1.1× and 1.9×; female individuals, 2.3× and 3.6×) for the 'PWH' cohort. The light blue diamond line represents lifetime AAD cumulative incidence if there was no disengagement from HIV care among PWH. The red triangle line represents the cumulative incidence of AAD when a 5 year forward-shift in both AAD incidence and non-HIV-related mortality were applied to capture the potential for premature aging among PWH. AAD, age-associated dementia; PWH, people with HIV.

from care and 2.2× AAD incidence rates, given higher non-HIV-related mortality estimated among female individuals with HIV (Fig. 3a, top right panel).

We also examined the impact of changes in non-HIV-related/non-AAD-related mortality and AAD incidence rates on the lifetime cumulative incidence of AAD among PWH (Fig. 3b). We projected that lifetime AAD cumulative incidence would rise among PWH as non-HIV-related/non-AAD-related mortality decreases and AAD incidence rates increase (bottom and right of Fig. 3B). Lifetime AAD cumulative incidence among male individuals with HIV would surpass the general population if non-HIV-related mortality was the same for PWH and the general population (RMR, 1.0) and AAD incidence rates among PWH were 1.4× the general population or if non-HIV-related mortality RMRs were 1.5 or less and AAD incidence was 2.0× the general population (Fig. 3b, bottom left panel). A similar pattern was observed for female individuals with HIV (Fig. 3b, bottom right panel).

Discussion

Using the previously validated CEPAC and AgeD-Pol simulation models together, we projected that 34.1% of

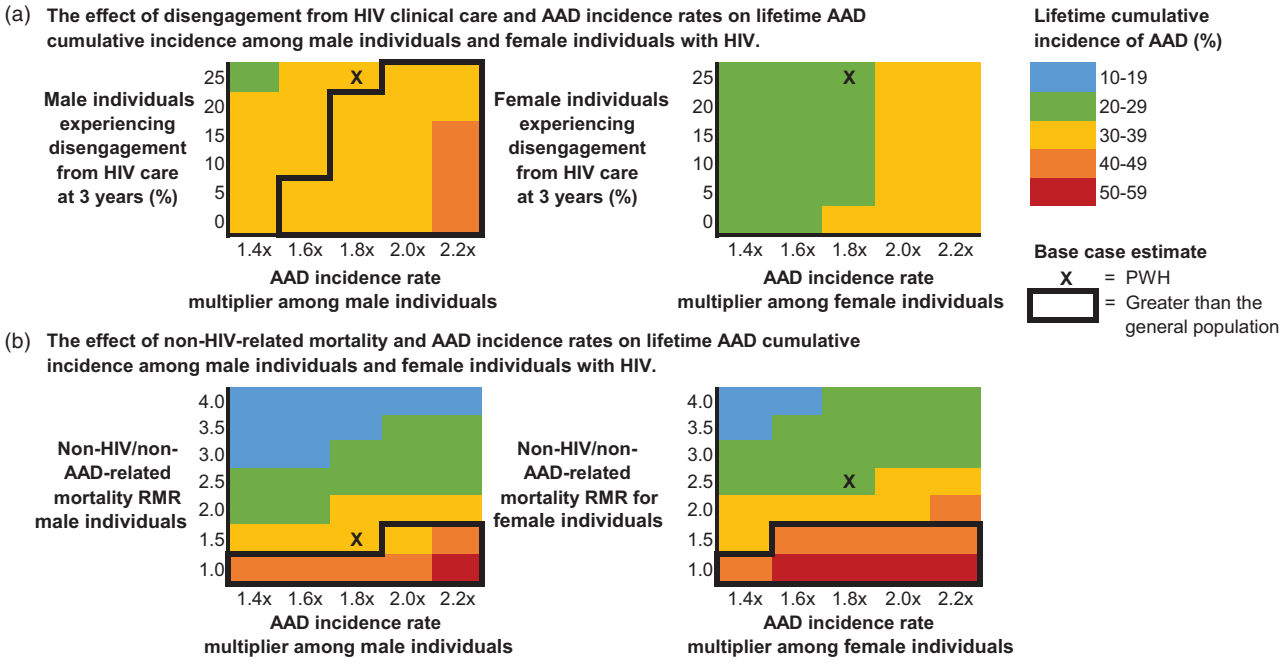

Fig. 3. Results from two-way sensitivity analyses: (panel a) the effect of disengagement from HIV clinical care and AAD incidence rates and (panel b) the effect of non-HIV/non-age-associated dementia-related mortality and AAD incidence rates on lifetime AAD cumulative incidence among PWH. Panel a shows the results of a two-way sensitivity analysis varying the percentage of male individuals (top left panel) and female individuals (top right panel) with HIV who are disengaged from HIV care at 3 years (*y*-axis) and AAD incidence rates (*x*-axis). The base case estimates for projected lifetime AAD cumulative incidence are marked with an 'X' (PWH); more cumulative incidence of AAD will occur at higher AAD incidence rates (right) and lower disengagement from care (bottom), as shown in orange. Model-projected lifetime AAD cumulative incidence within the black box are greater than published estimates for male individuals in the general US population. Published estimates of lifetime AAD cumulative incidence among female individuals from the general US population is 40.2%, which is not shown on the figure because it is greater than model-projections for PWH even with a 0% disengagement from HIV care at 3 years and 2.2-fold increase in age-stratified AAD incidence rates. Panel b shows the results of a two-way sensitivity analysis varying non-HIV-related/non-AAD-related mortality RMRs and AAD incidence rates among male individuals (bottom left panel) and female individuals (bottom right panel) with HIV. The base case estimates for projected lifetime AAD cumulative incidence are marked with an 'X' (PWH). A black box surrounds the model-projected lifetime AAD cumulative incidence that would be greater than published estimates for the general population. Lifetime AAD cumulative incidence increases at lower non-HIV-related mortality (bottom) and higher AAD incidence rates (right). AAD, age-associated dementias; PWH, people with HIV; RMR, relative mortality ratio.

male individuals and 27.5% of female individuals who are 60 years old and living with HIV would develop AAD over their lifetimes. Disparities in AAD cumulative incidence between people with and without HIV would increase later over a lifetime, reflecting the impact of higher competing risks of mortality among people with HIV. This trend is accentuated among female individuals with HIV compared with male individuals because female individuals with HIV often experience a substantially higher risk of non-HIV-related mortality compared with female individuals from the general population. We also found that parameters with a greater effect on life expectancy among people at 60 years, such as non-HIV-related mortality and rates of engagement in HIV care, had a substantial influence on the cumulative incidence of AAD. Among dementia-associated parameters, age-stratified/sex-stratified AAD incidence rates, which are known to be uncertain among people with HIV, substantially influenced lifetime AAD cumulative incidence.

Competing risks of mortality are key components of this model-based analysis. Shorter life expectancies among PWH than the general population are explained by the higher prevalence of smoking, substance use disorder, serious mental illness, and disadvantageous social determinants of health, as well as opportunistic infections that occur more frequently among PWH not on ART [20,52]. We found that lifetime AAD cumulative incidence was sensitive to these competing risks of mortality as PWH would be more likely to die at ages prior to the highest incidence of AAD [21–23,41]. Earlier initiation of less toxic, more effective ART regimens as per current guidelines could further reduce HIV-related mortality [54], as could efforts to improve non-HIV-related mortality such as tobacco cessation, statin use, and care for substance use disorder, among other initiatives. Most of this excess mortality was because of non-HIV-related mortality, given the smaller impact of improving engagement in care compared with reducing

estimates of non-HIV-related mortality among PWH. We found that this effect was more substantial among female individuals than male individuals with HIV, given the demographics of female individuals at highest risk for HIV acquisition [55–57], resulting in a lower model-projected lifetime AAD cumulative incidence among female individuals with diagnosed HIV compared with female individuals in the general population.

Even with increased non-HIV-related mortality compared with the general US population, over a quarter of PWH aged 60 years and older would develop AAD over their lifetimes in model projections. Because PWH have higher rates of tobacco use and increased risk of cardiovascular disease, they are likely to have a further increased risk of vascular and other related dementias [58,59]. One recent study showed that PWH have nearly double the AAD risk compared with people without HIV [6]. Accounting for this increased risk of AAD, we projected high cumulative AAD incidence among PWH despite increased competing mortality risks compared with the general population. We found that varying age-stratified AAD incidence rates or incorporating premature aging for PWH had a marked impact on the cumulative incidence of AAD but minimal impact on survival.

These results support a focus on further understanding the interplay between HIV and AAD, factors contributing to increased AAD risk among PWH, and the need for increased services for people aging with HIV. Improving engagement in care would reduce competing HIV-related mortality, which could, however, further increase the lifetime risk of developing AAD, unless interventions to reduce AAD risk are made available and accessible. Interventions to counter disadvantageous social determinants of health, reduce tobacco use, and treat substance use disorder are, therefore, essential to improve life expectancy and reduce the lifetime risk of AAD among people aging with HIV, such as has been investigated in the general population [60]. A published cost-effectiveness analysis showed that interventions aimed at lowering vascular risk factors, such as treating hypertension and smoking cessation, could be cost-effective in reducing dementia among the general population [61]. Similar analytic approaches are critical to study policies that can improve the health and lifespan of PWH.

PWH often encounter structural barriers to clinical care. Caregiver services in the United States are most often offered in traditional family structures with kinship networks as primary caregivers; many PWH may not be supported in traditional family structures [62,63]. In addition, population aging – due to an increase in the number of people 65 years and older and a decrease in the number of working-age people – will likely exacerbate this problem [64]. Further, national guidelines for the care of people with HIV do not include any specific guidance regarding the neurologic evaluation of people aging with HIV and offer no recommendations on best practices for cognitive impairment testing [54,65,66]. Additionally, many PWH experience stigma at facilities that care for older persons, where there might be less experience with HIV than traditional HIV-focused providers [67,68]. Our model-based results highlight the consideration needed when planning health systems support for people aging with HIV.

This analysis has several limitations. We focused on people living with diagnosed HIV as available estimates of dementia and HIV outcomes are limited to people already diagnosed with HIV. Estimates of AAD incidence and AAD-associated mortality among PWH are uncertain; we used the best available data regarding differences in AAD incidence for PWH compared with the general population. We varied these estimates in sensitivity and scenario analyses to provide a range of model projections and found that they converge on the single message of a rising cumulative AAD incidence in PWH that should inform healthcare planning. Available cohort data are disproportionately from White people; racial differences in AAD incidence and survival could affect model-projected outcomes. The past few years are notable for markedly increased non-HIV-related/non-AAD-related mortality in the United States (e.g. COVID-19 pandemic, opiate crisis); if these trends continue, life expectancy could further decline among PWH, which would influence the cumulative incidence of AAD [69]. Finally, we intentionally do not attempt to isolate the incidence and outcomes of HAND in this analysis, given the lack of clear diagnostic criteria [70], although the increased risk of dementia diagnoses among PWH could include some diagnoses of HAND [6]. Mild and moderate cognitive impairment is evident in approximately 30–50% of PWH [71], which might not be captured in these model projections of AAD.

In summary, with HIV clinical care dramatically reducing HIV-related mortality in the United States, people with HIV are now at risk for developing age-associated dementia as they survive to older ages. It is critical to improve screening, diagnosis, and treatment of dementia among people aging with HIV. Differences in mortality risks and support structures for PWH should be considered when coordinating AAD and HIV prevention and mitigation efforts. This analysis provides insights to inform decision-makers and health systems planning for people aging with HIV.

Acknowledgements

We thank Ms. Yiqi Qian for technical assistance updating input parameters to 2019.

Author contributions: E.P.H., J.H.A.F., and N.W. designed the study. E.P.H., J.H.A.F., F.M.S., Y.Q., L.Y.,

and N.W. collected, interpreted, and handled the data. E.P.H., J.H.A.F., N.W., and A.T. performed the analysis and drafted the manuscript. E.P.H., S.S.M., P.E.S., L.H.R., A.V., L.H.S., and K.A.F. provided clinical expertise. All co-authors provided critical revisions of the manuscript. All authors have read and approved the final version of the article.

Funding: this work was supported by the National Institute of Allergy and Infectious Diseases [R01AI042006 (K.A.F.); R01AI093269 (K.P.R.); U01AI069918 (K.N.A.)], the National Institute on Aging [R01AG069575 (E.P.H.); R56AG074839 (K.N.A.)], the National Institutes of Health [R01AG047975, R01AG026484, P50AG005134 (A.V.); K23MH115812, R01MH131194 (S.M.)], the JHU Center for the Advancement of Neurotherapeutics [JHU CAHN, P30 MH075673 (L.R.)], the Rappaport Fellowship (S.M.), the Steve and Deborah Gorlin MGH Research Scholars Award (K.A.F.), and the MGH Jerome and Celia Reich Endowed Scholar Award (E.P.H.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Massachusetts General Hospital.

Role of funding source: the funding sources had no role in the design, analysis, or interpretation of the study, the writing of the manuscript, or in the decision to submit the manuscript for publication.

Conflicts of interest

There are no conflicts of interest.

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