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Impact on life expectancy of HIV-1 positive individuals of CD4⁺ cell count and viral load response to antiretroviral therapy

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HIV Cohort (UK CHIC) Study

Objective: The objective of this study is to estimate life expectancies of HIV-positive patients conditional on response to antiretroviral therapy (ART).

Methods: Patients aged more than 20 years who started ART during 2000–2010 (excluding IDU) in HIV clinics contributing to the UK CHIC Study were followed for mortality until 2012. We determined the latest CD4⁺ cell count and viral load before ART and in each of years 1–5 of ART. For each duration of ART, life tables based on estimated mortality rates by sex, age, latest CD4⁺ cell count and viral suppression (HIV-1 RNA <400 copies/ml), were used to estimate expected age at death for ages 20–85 years.

Results: Of 21 388 patients who started ART, 961 (4.5%) died during 110 697 person-years. At start of ART, expected age at death [95% confidence interval (CI)] of 35-year-old men with CD4⁺ cell count less than 200, 200–349, at least 350 cells/μl was 71 (68–73), 78 (74–82) and 77 (72–81) years, respectively, compared with 78 years for men in the general UK population. Thirty-five-year-old men who increased their CD4⁺ cell count in the first year of ART from less than 200 to 200–349 or at least 350 cells/μl and achieved viral suppression gained 7 and 10 years, respectively. After 5 years on ART, expected age at death of 35-year-old men varied from 54 (48–61) (CD4⁺ cell count <200 cells/μl and no viral suppression) to 80 (76–83) years (CD4⁺ cell count ≥350 cells/μl and viral suppression).

Conclusion: Successfully treated HIV-positive individuals have a normal life expectancy. Patients who started ART with a low CD4⁺ cell count significantly improve their life expectancy if they have a good CD4⁺ cell count response and undetectable viral load.

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Introduction

Life expectancy of HIV-positive individuals treated with antiretroviral therapy (ART) in the UK improved by nearly 16 years between 1996 and 2008 [1]. Although some groups of HIV-positive individuals may expect to live a similar life span to that of the general population, others have reduced life expectancy due to the impact of late diagnosis and late initiation of ART [1,2]. A previous study estimated life expectancies of HIV patients in the UK stratified by CD4⁺ cell count at ART start [1], but not gains in years of life in response to ART [1]. A European study showed that successfully treated patients who attained a CD4⁺ cell count more than 500 cells/ μ l have a standardized mortality ratio (SMR) approaching 1 [3]. However, SMRs are more difficult to communicate to patients than life expectancies and not all patients attain a CD4⁺ cell count more than 500 cells/ μ l [4,5]. The lower limit of the normal CD4⁺ cell count range is below 500 cells/ μ l, and therefore exceeding this level might be an unrealistic target for patients who had low preinfection counts [6]. Furthermore, viral suppression is an important factor in treatment success [7] and virological replication may have an effect on prognosis that is independent of CD4⁺ cell count [8,9].

We aimed to investigate the improvement in life expectancy due to CD4⁺ cell count restoration and viral suppression in patients on ART. We used data from the UK Collaborative HIV Cohort (UK CHIC) Study, on HIV-positive individuals in care in the UK between 2000 and 2012, to estimate life expectancy of those treated for HIV-infection at different durations of ART according to latest CD4⁺ cell count and viral suppression status.

Materials and methods

Cohort description

The UK CHIC Study was initiated in 2001 and collates routine data on HIV-positive individuals aged 16 years or over attending clinical centres in the UK since 1 January 1996 (see appendix) [10]. The project uses anonymized data and was approved by a Multicentre Research Ethics Committee and by local ethics committees.

Patient selection

Patients included in this analysis were aged 20 years and over and started treatment with ART with at least three drugs between 1 January 2000 and 31 December 2010 and were followed up until 31 December 2012. Individuals whose assumed transmission was via injection drug use or mother-to-child were excluded due to low frequencies and worse prognosis compared with other risk groups. Patients with missing baseline CD4⁺ cell count were included in the study population. Patients were followed up from ART start for all-cause mortality.

Deaths were ascertained from clinic records and by linkage to national surveillance data that use the UK civil death registry. Patients were considered lost to follow-up if they did not have a visit date within 2 years of database close date and were not known to have died before 31 December 2012. Those lost to follow-up were censored at the date of the last visit plus 3 months. Crude rate of losses to follow-up was determined and characteristics of patients who were and were not lost to follow-up were compared.

Variable measurements

The latest CD4⁺ cell count before starting ART and the last measured in the first, second, third, fourth and fifth year of ART were determined for patients remaining in follow-up. We determined whether patients were virally suppressed (HIV-1 RNA <400 copies/ml) in the previous year for those remaining under follow-up. For the first year of ART, we used measurements of viral load from 6 to 12 months duration of ART.

Statistical methods

Crude sex-specific mortality rates (per 1000 person-years) were calculated overall and for those aged 20–44 years. Six Poisson models were used to estimate mortality rates from start of ART and for each duration of ART (follow-up starting at 0, 1, 2, 3, 4 and 5 years after ART start), by sex, age, latest CD4⁺ cell count (<200, 200–349, \geq 350 cells/ μ l) and viral load (\leq 400 versus >400 copies/ml). Abridged life tables were constructed for each sex from age-specific mortality rates grouped in 5-year age bands and used to estimate life expectancy for ages 20–85 years. These tables describe the mortality experience that hypothetical cohorts of HIV-positive individuals would have if they were subjected to the mortality in the observed period. Life expectancy at an exact age is defined as the average number of years remaining among individuals who survived to the specified age, according to the cross-sectional age-specific all-cause mortality rates during the study period. In this article, we present expected age at death instead of life expectancy, as clinicians and patients have indicated a preference for this. For example, if a 35-year-old has a life expectancy of 40 years, their expected age at death would be 75 years old. The main analyses estimated expected age at death [95% confidence interval (95% CI)] for each sex overall, and stratified by both achieved CD4⁺ cell count and viral suppression status at exact ages 20, 35 and 50 years old. Secondary analyses estimated the effect on expected age at death of attained CD4⁺ cell count unadjusted for viral suppression and vice versa.

We used sex-specific mortality rates in the UK population for 2000–2009 grouped in 5-year age bands to estimate life expectancies of the general population (www.mortality.org). Life expectancies were compared for those with attained CD4⁺ cell count 350–499 versus at least 500 cells/ μ l. Detailed information on the calculation of

life tables has been published previously [2]. We used Stata version 12 and Microsoft Excel 2008 to perform analyses.

Results

The UK CHIC Study included data on 47 201 HIV-positive individuals of whom 22 151 started ART between 2000 and 2010. We excluded 568 (3%) IDU, 164 (0.7%) infected via mother-to-child transmission, two patients without sex recorded and 29 aged less than 20 years, which left 21 388 eligible patients.

Table 1 summarizes the demographic and clinical characteristics of patients at ART start by sex and the proportion of patients with missing data for each covariate. The majority of patients 14 742/21 388 (69%) were men, and of these, 10 246 (71%) were MSM, and 9649 (67%) were of white ethnicity. In contrast, nearly all the women 6265/6646 (97%) were infected heterosexually and the majority 4778 (74%) were

black African. The women were younger than the men with very few aged 60 years or more.

During 110 697 person-years, 961/21 388 (4.5%) patients died. The crude mortality rate of 9.0 per 1000 person-years for men (95% CI 8.4–9.7) was higher than rate of 7.9 for women (7.0–8.9), but was the same in both sexes for those aged less than 45 years [men 6.9 (6.2–7.7); women 6.9 (6.0–7.9)]. Rate of losses to follow-up was 3.9 per 100 person-years. Compared with those retained in care, patients lost to follow-up were more likely to be men, infected through heterosexual contact or blood (or unknown), black African, Asian or mixed race (or unknown), younger, diagnosed with AIDS prior to starting ART and had higher CD4⁺ cell count at ART start, although median CD4⁺ cell count was similar [retained in care 214 interquartile range (IQR) 116–310; lost 210 (108–320) cells/μl]. For the analyses taking into account response to treatment in the first, second, third, fourth and fifth years after starting ART, data were available on 16 794/19 855 (85%), 15 604/17 400 (90%), 13 223/14 721 (90%), 11 032/12 201 (90%) and 9126/

Table 1. Demographic and clinical characteristics of patients at start of antiretroviral therapy by sex (N = 21 388).

Variable N (%)	Missing N (%)	Men (N = 14742)	Missing N (%)	Women (N = 6646)
Ethnicity	375 (2.5)		170 (2.6)	
White		9649 (67.2)		730 (11.3)
Black African		2527 (17.6)		4778 (73.8)
Other		2191 (15.3)		968 (15.0)
Age distribution (years)	–		–	
<30		2214 (15.0)		1915 (28.8)
30–39		6343 (43.0)		3000 (45.1)
40–49		4435 (30.1)		1260 (19.0)
50–59		1290 (8.8)		357 (5.4)
≥60		460 (3.1)		114 (1.7)
Age median (IQR) (years)		38 (32–44)		34 (29–40)
Risk factor for transmission	364 (2.5)		166 (2.5)	
MSM		10 246 (71.3)		–
Heterosexual		3531 (24.6)		6265 (96.7)
Blood		64 (0.4)		32 (0.5)
Other		537 (3.7)		183 (2.8)
AIDS CDC stage C diagnosis	–	2158 (14.6)	–	1059 (15.9)
CD4 ⁺ cell count distribution (cells/μl)	2080 (14.1)		1086 (16.3)	
<200		7035 (49.2)		2746 (49.4)
200–349		4876 (34.1)		1734 (31.2)
≥350		2375 (16.6)		1080 (19.4)
CD4 ⁺ cell count Median (IQR)		220 (121–313)		200 (100–310)
HIV-1 RNA (log copies/ml)	2082 (14.1)		1150 (17.3)	
<4.00		2899 (22.9)		2050 (37.3)
4.00–4.99		4485 (35.4)		1937 (35.2)
≥5.00		5276 (41.7)		1509 (27.5)
HIV-1 RNA Median (IQR)		4.8 (4.1–5.3)		4.4 (3.4–5.1)
Initial drug regimen	–		–	
PI-based		3325 (22.6)		2053 (30.9)
NNRTI-based		10 157 (68.9)		4102 (61.7)
Triple NRTI		295 (2.0)		202 (3.0)
Four or more drugs		736 (5.0)		231 (3.5)
Nonstandard regimen		229 (1.6)		58 (0.9)
Year of starting ART	–		–	
2000–2002		3046 (20.7)		1484 (22.3)
2003–2005		3763 (25.5)		2013 (30.3)
2006–2008		4652 (31.6)		1974 (29.7)
2009–2010		3281 (22.3)		1175 (17.7)

ART, antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

10 030 (91%) patients, respectively, who had appropriate CD4⁺ cell count and viral load measurements in those years and had subsequent follow-up time.

Overall estimates of expected age at death from antiretroviral therapy start compared with the UK general population

The expected age at death for HIV-positive men from ART start was 68 (66–71), 73 (71–76) and 77 (75–80) years at exact ages 20, 35 and 50 years, respectively, compared with 77, 78 and 79 years in the general population. The corresponding expected age at death for HIV-positive women was 69 (65–73), 74 (70–78) and 78 (73–82) years, compared with 81, 82 and 83 years in the general population.

Effect of CD4⁺ cell count and viral suppression on life expectancies

Expected age at death (95% CI) for men (Table 2) and women (Table 3) showed a graded association with both attained CD4⁺ cell count and viral suppression status. At ART start, a 35 year-old man with CD4⁺ cell count less than 200 cells/ μ l could expect to live to 71 (68–73) years, over 7 years less than men in the general UK population. Such a patient who achieved viral suppression and increased their CD4⁺ cell count in the first year of ART to 200–349 or at least 350 cells/ μ l increased their expected age at death to 78 (74–82) or 81 (77–84) years, respectively. This is comparable with the general population male life expectancy of 78 years. After 5 years on ART, expected age at death of 35-year-old men varied from 54 (48–61) to 80 (76–83) years for those with CD4⁺ cell count less than 200 cells/ μ l and no viral suppression versus CD4⁺ cell count at least 350 cells/ μ l and suppressed. Figures 1 (men) and 2 (women) illustrate that within each CD4⁺ cell count strata, expected age at death is higher for those with than those without viral suppression.

Compared with men at ART start, the expected age at death was between 3 and 4 years greater for those who survived 5 years on ART (Table 2), depending on their current age. Life expectancy was higher for women reflecting the higher life expectancy of women in the general population (Table 3). There was no difference in mortality between those with CD4⁺ cell count 350–499 and at least 500 cells/ μ l for either men or women.

Median CD4⁺ cell count increased with duration of ART and was higher in those with viral suppression (Supplementary figure 1, <http://links.lww.com/QAD/A495>). The proportion of patients with CD4⁺ cell count at least 350 cells/ μ l increased markedly in the first year of ART, and continued to increase up to 5 years on ART (Supplementary figure 2, <http://links.lww.com/QAD/A495>). Only 19% of patients had CD4⁺ cell count more than 350 cells/ μ l at ART start, compared with 79% of

patients on ART for more than 5 years, with 52% having CD4⁺ cell count more than 500 cells/ μ l.

Mortality rates per 1000 person years among younger men decreased with increasing CD4⁺ cell count and were lower in patients with viral suppression. Mortality rates overall, and restricted to those aged 20–44 years, for different durations of ART, and stratified by CD4⁺ cell count and viral suppression, are summarized in supplementary Tables 4 (men) and 5 (women), <http://links.lww.com/QAD/A495>. After 5 years on ART, mortality rates among younger men varied from 2.7 (1.7–4.3) (viral suppression/high CD4⁺ cell count) to 38.1 (21.1–68.9) (unsuppressed/low CD4⁺ cell count). Of those who died, 20% did not have a clinic visit recorded in the previous 6 months and 11% had been out of care for more than 1 year.

Secondary analyses show the contributions of viral suppression unadjusted for CD4⁺ cell count (supplementary table 6, <http://links.lww.com/QAD/A495>) and CD4⁺ cell count unadjusted for viral suppression (supplementary table 7, <http://links.lww.com/QAD/A495>) to decrease in life expectancy of men. After 5 years on ART, 20-year-old men would be expected to live on average to age 75 years if virally suppressed and to 59 years without suppression. Viraemia at the previous visit was undetectable in 88% of patients on ART for 5 years. Compared to 20 year-old men with viral suppression, those without viral suppression had life expectancies that were 11 and 16 years shorter after 1 and 5 years of ART, respectively.

At ART start, 20-year-old men with CD4⁺ cell count less than 200, 200–349, at least 350 cells/ μ l were estimated to live on average to 65 (61–68), 74 (69–79) and 72 (67–77) years, respectively. After 5 years on ART, expected age at death was 50 (38–63), 72 (64–79) and 75 (70–81) years depending on whether their attained CD4⁺ cell count was less than 200, 200–349 or at least 350 cells/ μ l, respectively (supplementary table 7, <http://links.lww.com/QAD/A495>). Patterns for women were similar (data not shown).

Discussion

Successfully treated patients who achieved viral suppression and attained a CD4⁺ cell count of at least 350 cells/ μ l within 1 year of starting ART had a normal life expectancy, with a 35-year-old HIV-positive person estimated to live to about 80 years on average. Patients with CD4⁺ cell count less than 200 cells/ μ l, either before or after starting ART, were at an increased risk of death: the difference in life expectancy between those with attained CD4⁺ cell count less than 200 compared with at least 200 cells/ μ l was 8 years at ART start and widened

Table 2. Expected age at death (95% confidence interval) of men stratified by viral suppression and attained CD4⁺ cell count at 1, 2, 3, 4 and 5 years after start of antiretroviral therapy.

	HIV-1 RNA (copies/ml) ≤400						HIV-1 RNA (copies/ml) >400					
	CD4 ⁺ cell count <200 cells/μl		CD4 ⁺ cell count 200–349 cells/μl		CD4 ⁺ cell count ≥350 cells/μl		CD4 ⁺ cell count <200 cells/μl		CD4 ⁺ cell count 200–349 cells/μl		CD4 ⁺ cell count ≥350 cells/μl	
	All men ^a											
From start of ART												
No. of deaths/patients (%)												
EAD at exact age												
20 years	75/1308 (5.7)	85/2955 (2.9)	125/6383 (2.0)	74 (69–80)	78 (73–82)	78 (73–82)	370/5507 (6.7)	136/4769 (2.9)	69/2386 (2.9)	686/14742 (4.6)		
35 years	65 (58–72)	74 (69–80)	78 (73–82)	71 (67–74)	81 (77–84)	81 (77–84)	65 (61–68)	74 (69–79)	72 (67–77)	68 (66–71)		
50 years	76 (72–79)	81 (77–85)	83 (79–87)	76 (72–79)	83 (79–87)	83 (79–87)	71 (68–73)	78 (74–82)	77 (72–81)	73 (71–76)		
							76 (73–79)	81 (77–86)	80 (76–85)	77 (75–80)		
From 1 year after ART start												
No. of deaths/patients (%)												
EAD at exact age												
20 years	36/617 (5.8)	56/2112 (2.7)	111/6711 (1.7)	74 (69–80)	78 (74–83)	78 (74–83)	44/342 (12.9)	24/388 (6.2)	24/545 (4.4)	377/11921 (3.2)		
35 years	61 (51–71)	74 (69–80)	78 (74–83)	65 (58–72)	81 (77–84)	81 (77–84)	52 (43–62)	64 (54–73)	67 (59–75)	71 (67–75)		
50 years	68 (64–72)	81 (77–84)	83 (79–87)	76 (72–79)	83 (79–87)	83 (79–87)	61 (56–67)	70 (63–76)	72 (66–78)	75 (72–78)		
	73 (69–77)	81 (77–84)	83 (79–87)	76 (72–79)	83 (79–87)	83 (79–87)	69 (63–76)	75 (78–81)	77 (70–84)	79 (76–81)		
From 2 years after ART start												
No. of deaths/patients (%)												
EAD at exact age												
20 years	38/251 (15.1)	22/373 (5.9)	16/655 (2.4)	74 (68–81)	77 (72–81)	77 (72–81)	53/322 (16.5)	20/463 (4.3)	19/742 (2.6)	295/10967 (2.7)		
35 years	57 (45–69)	74 (68–81)	77 (72–81)	68 (64–72)	81 (77–84)	81 (77–84)	49 (39–58)	64 (55–74)	69 (61–76)	72 (68–77)		
50 years	65 (59–70)	77 (73–82)	80 (76–84)	73 (69–77)	81 (77–84)	83 (79–87)	58 (53–64)	70 (63–77)	73 (67–80)	76 (73–79)		
	71 (66–76)	80 (76–84)	82 (78–86)	73 (69–77)	81 (77–84)	83 (79–87)	67 (60–74)	75 (69–81)	77 (71–84)	79 (76–82)		
From 3 years after ART start												
No. of deaths/patients (%)												
EAD at exact age												
20 years	15/220 (6.8)	35/1112 (3.1)	82/5300 (1.5)	74 (68–81)	77 (72–81)	77 (72–81)	21/337 (6.2)	39/1526 (2.6)	102/6056 (1.7)	238/9198 (2.6)		
35 years	55.2 (6.2)	73 (66–79)	79 (74–84)	65 (59–70)	80 (76–83)	80 (76–83)	46 (36–57)	66 (57–75)	69 (61–77)	72 (67–76)		
50 years	64 (56–71)	77 (71–81)	82 (77–86)	71 (66–76)	80 (76–84)	82 (78–86)	57 (51–62)	71 (65–77)	74 (67–80)	76 (73–79)		
	71 (64–78)	80 (75–85)	84 (80–88)	71 (66–76)	80 (76–84)	82 (78–86)	66 (59–73)	76 (69–83)	77 (71–84)	79 (76–82)		
From 4 years after ART start												
No. of deaths/patients (%)												
EAD at exact age												
20 years	9/152 (5.9)	18/829 (2.2)	69/4464 (1.5)	74 (68–79)	77 (71–81)	77 (72–81)	28/179 (15.6)	7/250 (2.8)	12/523 (2.3)	179/7584 (2.4)		
35 years	55.2 (6.2)	73 (66–79)	79 (74–84)	64 (56–71)	80 (75–85)	84 (80–88)	45.2 (6.7)	64.3 (5.7)	71 (62–80)	72 (67–77)		
50 years	71 (64–78)	80 (75–85)	84 (80–88)	71 (64–78)	80 (75–85)	84 (80–88)	56 (50–62)	70 (63–78)	75 (68–82)	76 (73–80)		
	9/152 (5.9)	18/829 (2.2)	69/4464 (1.5)	71 (64–78)	80 (75–85)	84 (80–88)	66 (58–74)	75 (68–82)	79 (73–85)	80 (76–83)		
From 5 years after ART start												
No. of deaths/patients (%)												
EAD at exact age												
20 years	57.0 (6.5)	73 (66–81)	77 (72–82)	64 (56–71)	77 (71–82)	80 (76–83)	42.8 (6.8)	61.3 (5.7)	65.6 (5.1)	72 (67–78)		
35 years	65 (57–73)	77 (71–82)	80 (76–83)	71 (65–79)	80 (75–85)	82 (78–86)	54 (48–61)	68 (60–75)	71 (75–77)	77 (73–80)		
50 years	71 (65–79)	80 (75–85)	82 (78–86)	71 (65–79)	80 (75–85)	82 (78–86)	64 (56–73)	73 (66–80)	76 (69–82)	80 (76–84)		

ART, antiretroviral therapy; EAD, expected age at death.
^aIncludes men without a CD4⁺ cell count at start of ART.

Table 3. Expected age at death (95% confidence interval) of women stratified by viral suppression and attained CD4⁺ cell count at 1, 2, 3, 4 and 5 years after start of antiretroviral therapy.

	HIV-1 RNA (copies/ml) ≤400						HIV-1 RNA (copies/ml) >400						
	CD4 ⁺ cell count <200 cells/μl		CD4 ⁺ cell count 200–349 cells/μl		CD4 ⁺ cell count ≥350 cells/μl		CD4 ⁺ cell count <200 cells/μl		CD4 ⁺ cell count 200–349 cells/μl		CD4 ⁺ cell count ≥350 cells/μl		
													All women
From start of ART													
No. of deaths/patients (%)													
EAD at exact age													
20 years	60 (48–72)	77 (70–84)	81 (75–86)	79 (74–85)	50 (39–60)	69 (60–77)	72 (63–80)	74 (66–82)	75 (69–81)	77 (71–83)	74 (66–82)	77 (73–82)	74 (69–79)
35 years	67 (58–76)	80 (74–85)	83 (78–88)	81 (76–86)	59 (52–66)	73 (66–80)	75 (68–82)	78 (70–85)	78 (74–83)	76 (69–82)	79 (72–85)	80 (76–84)	77 (73–82)
50 years	73 (65–80)	82 (77–88)	85 (79–90)	83 (78–89)	68 (59–76)	77 (70–84)	79 (72–85)	81 (74–87)	81 (76–86)	79 (70–84)	81 (74–87)	80 (76–84)	81 (76–86)
From 1 year after ART start													
No. of deaths/patients (%)													
EAD at exact age													
20 years	68 (60–76)	77 (71–84)	81 (74–87)	79 (74–85)	50 (39–60)	69 (60–77)	72 (63–80)	74 (66–82)	75 (69–81)	77 (71–83)	74 (66–82)	77 (73–82)	74 (69–79)
35 years	73 (68–79)	81 (75–86)	83 (78–89)	81 (76–86)	59 (52–66)	73 (66–80)	75 (68–82)	78 (70–85)	78 (74–83)	76 (69–82)	79 (72–85)	80 (76–84)	77 (73–82)
50 years	77 (72–83)	83 (77–89)	85 (79–91)	83 (78–89)	68 (59–76)	77 (70–84)	79 (72–85)	81 (74–87)	81 (76–86)	79 (70–84)	81 (74–87)	80 (76–84)	81 (76–86)
From 2 years after ART start													
No. of deaths/patients (%)													
EAD at exact age													
20 years	64 (54–74)	77 (70–84)	81 (75–86)	79 (74–85)	50 (39–60)	69 (60–77)	72 (63–80)	74 (66–82)	75 (69–81)	77 (71–83)	74 (66–82)	77 (73–82)	74 (69–79)
35 years	70 (63–77)	80 (74–85)	83 (78–88)	81 (76–86)	59 (52–66)	73 (66–80)	75 (68–82)	78 (70–85)	78 (74–83)	76 (69–82)	79 (72–85)	80 (76–84)	77 (73–82)
50 years	75 (68–82)	82 (77–88)	85 (79–90)	83 (78–89)	68 (59–76)	77 (70–84)	79 (72–85)	81 (74–87)	81 (76–86)	79 (70–84)	81 (74–87)	80 (76–84)	81 (76–86)
From 3 years after ART start													
No. of deaths/patients (%)													
EAD at exact age													
20 years	64 (54–74)	77 (70–84)	81 (75–86)	79 (74–85)	50 (39–60)	69 (60–77)	72 (63–80)	74 (66–82)	75 (69–81)	77 (71–83)	74 (66–82)	77 (73–82)	74 (69–79)
35 years	70 (63–77)	80 (74–85)	83 (78–88)	81 (76–86)	59 (52–66)	73 (66–80)	75 (68–82)	78 (70–85)	78 (74–83)	76 (69–82)	79 (72–85)	80 (76–84)	77 (73–82)
50 years	75 (68–82)	82 (77–88)	85 (79–90)	83 (78–89)	68 (59–76)	77 (70–84)	79 (72–85)	81 (74–87)	81 (76–86)	79 (70–84)	81 (74–87)	80 (76–84)	81 (76–86)
From 4 years after ART start													
No. of deaths/patients (%)													
EAD at exact age													
20 years	60 (48–72)	76 (69–84)	82 (76–88)	82 (76–88)	49 (38–60)	68 (58–77)	74 (66–82)	75 (69–81)	75 (69–81)	74 (66–82)	75 (69–81)	75 (69–81)	75 (69–81)
35 years	67 (58–76)	79 (73–85)	84 (79–89)	84 (79–89)	59 (51–67)	73 (66–80)	78 (70–85)	78 (74–83)	78 (74–83)	76 (69–82)	78 (70–85)	79 (73–82)	78 (74–83)
50 years	73 (65–80)	82 (76–87)	86 (81–92)	86 (81–92)	68 (59–77)	77 (70–84)	81 (74–87)	81 (76–86)	81 (76–86)	79 (70–84)	81 (74–87)	81 (76–86)	81 (76–86)
From 5 years after ART start													
No. of deaths/patients (%)													
EAD at exact age													
20 years	64 (51–76)	78 (72–86)	82 (76–88)	82 (76–88)	50 (38–62)	68 (58–78)	71 (63–80)	71 (63–80)	71 (63–80)	71 (63–80)	71 (63–80)	71 (63–80)	77 (71–83)
35 years	70 (60–79)	81 (75–87)	84 (79–89)	84 (79–89)	59 (51–68)	73 (64–81)	75 (68–83)	75 (68–83)	75 (68–83)	75 (68–83)	75 (68–83)	75 (68–83)	81 (75–86)
50 years	75 (67–83)	83 (78–89)	86 (80–91)	86 (80–91)	68 (60–76)	77 (70–84)	79 (72–86)	79 (72–86)	79 (72–86)	79 (72–86)	79 (72–86)	79 (72–86)	83 (78–89)

ART, antiretroviral therapy; EAD, expected age at death.

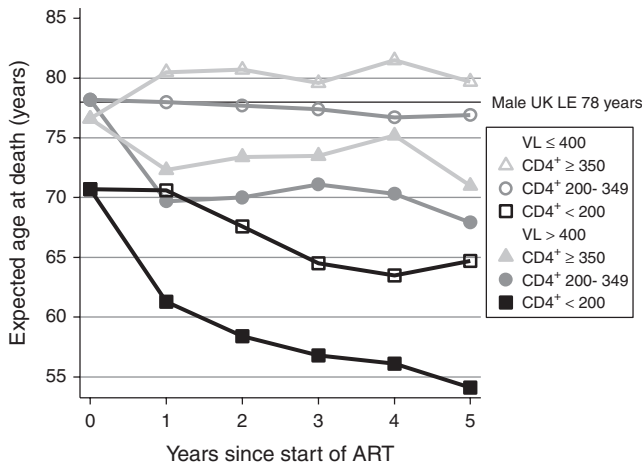


Fig. 1. Expected age at death of men aged 35 years at different durations of antiretroviral therapy according to current CD4⁺ cell count and viral suppression compared with the general population.

with duration of ART. Although most of the effect of viral suppression on decreasing mortality is likely to be mediated through increasing CD4⁺ cell count, nevertheless there remained an independent effect of detectable viral load on life expectancy. Those with CD4⁺ cell count less than 200 cells/ μ l at 5 years after starting ART lost between 15 and 26 potential years of life depending on whether they were or were not virally suppressed.

Strengths and limitations of study

We analysed data on over 20 000 patients on ART, among whom there were nearly a thousand deaths. Our study was based on a cohort that included approximately 34% of patients in usual care for HIV infection in UK and therefore our estimates of expected age at death should be applicable to patients on ART in the UK. In 2012–2013, UK CHIC undertook extensive linkage with databases

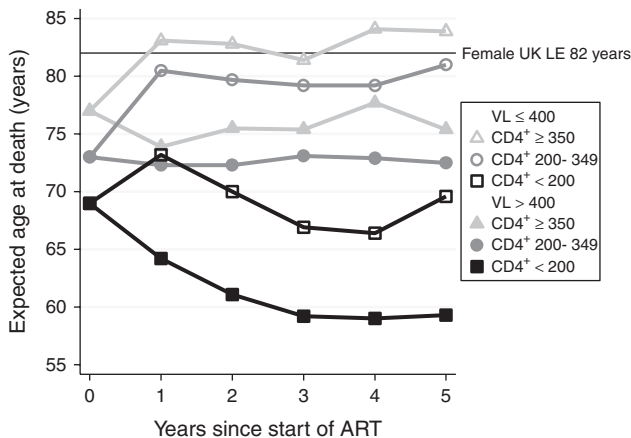


Fig. 2. Expected age at death of women aged 35 years at different durations of antiretroviral therapy according to current CD4⁺ cell count and viral suppression compared with the general population.

held at Public Health England (PHE) in order to validate the reporting of deaths by the participating hospital clinics and to include deaths missing from HIV clinic records (approximately 16% of all deaths), which were reported in the UK civil death register. Therefore completeness of death ascertainment should be high [11]. However, as many patients were lost to follow-up, there remains the possibility of missed deaths, which would bias estimates of expected age at death upwards. As expected, patients lost to follow-up were more likely to have characteristics associated with migrant backgrounds and some may have returned to their country of origin now that ART is more widely available, particularly in sub-Saharan Africa. Analyses of those lost to follow-up were inconclusive in determining whether lost patients were likely to have lower or higher mortality than those remaining in care. Reasons for losses to follow-up are varied and as well as including dropping out of care and deportation, also include transferring care to another ART provider, either in the UK, but not contributing to UK CHIC, or abroad. Although there was some evidence that, compared with those who remained in the study, those who dropped out were sicker (positive association with AIDS diagnosis), other associations implied that a well group were also lost to follow-up (younger and having a higher CD4⁺ cell count). As in a French study [12], men were more likely to be lost than women, which could be because men are a more mobile population. In each time period considered, only patients with data on CD4⁺ cell count and viral load measurements could be included, which led to around 10% of patients being excluded from each model. Therefore, our results may only apply to patients remaining in regular care in the UK, but this will be the majority of HIV-positive individuals in the continuum of care [13]. Our estimates of life expectancy only used age and sex-adjusted estimates of mortality rates that were stratified by response to ART determined by attained CD4⁺ cell count and viral suppression status. A greater range of variables, including non-HIV biomarkers, have been used in prognostic models that aim to define short-term prognosis rather than cancy [7,14–17].

Estimated life expectancy may be biased by extrapolation beyond available data. There were few patients aged more than 60 years (<3% of the total) and therefore estimates of mortality rates at older ages are imprecise, particularly in women. We compensated for this by using Poisson regression models to estimate mortality rates, which borrowed strength from trends across age and sex. Thus, we ensured that the rates used in lifetables were smoother than crude sex and age-specific rates would have been. However, this also constrained mortality patterns to be similar for men and women, which may not be true. In using lifetables, we are assuming that age-specific mortality rates estimated from the current population can be used as if they will apply within individuals throughout their lives. However, these estimates are based on a population that has experienced a maximum

duration of ART of 12 years, whereas a current patient who starts ART at age 35 years will, for example, when they are aged 60 experience the mortality rates of a 60 year-old conditional on having taken ART for 25 years. Possible scenarios that have been considered in a modelling exercise are that there will be long-term toxic effects of ART or that patients will run out of treatment options due to drug resistance [18]. On the contrary, in the future, better ART drugs may be developed or less toxic combinations used. In particular, NRTI-sparing regimens may reduce long-term toxicities. Currently, there is considerable interest and ongoing trials in ART simplification strategies [19], such as using a single boosted protease inhibitor as a maintenance regimen in those who are stable and virologically suppressed on ART [20], which will also reduce the cost of lifelong ART.

Discussion of findings in context

In response to the Health and Social Care Act 2012 [21], PHE has implemented a new scheme for monitoring the success of ART, which assesses both the proportion of patients with viral suppression and the proportion with CD4⁺ cell count at least 350 cells/ μ l; our study shows that both are associated with mortality risk and lost years of life. Although better immunological function is critical for avoiding AIDS-related mortality and may be important for avoiding some non-AIDS cancers [22–24], the inflammatory effect of viral replication may be also be associated with excess mortality, and in particular the SMART study showed an increased risk from cardiovascular disease with higher levels of interleukin-6, C-reactive protein and D-dimer [25]. Mendelian randomization studies suggest that interleukin-6 [26], but not C-reactive protein [27], is causally associated with coronary heart disease in the general population. Further research is required to establish whether any of the associations of these biomarkers of inflammation with mortality are causal in HIV-infected populations.

During the study period, guidelines recommended starting ART once CD4⁺ cell count had fallen below 350 cells/ μ l unless treatment was required for prevention of mother-to-child transmission or in the case of an AIDS diagnosis or other particular health need [28]. This explains the paradoxical finding that life expectancy from ART start was lower in those who started with CD4⁺ cell count at least 350 compared with 200–349 cells/ μ l; they would have been a highly selected group. However, with the move towards treatment as prevention [29] and the change in WHO guidelines to starting at CD4⁺ cell count below 500 cells/ μ l [30], it is likely that more people in the UK will start ART at higher CD4⁺ cell count even if asymptomatic. The current 2012 British HIV Association guidelines [31] continue to recommend that ART is started once CD4⁺ cell count has fallen below 350 cells/ μ l but allow for treatment above this threshold

to reduce the risk of transmission to partners if the patient wishes to start ART.

The predicted longevity is dependent on successfully navigating the continuum of care, which requires diagnosis of HIV infection before severe immunosuppression, prompt linkage to care, timely initiation of treatment, good adherence to ART and retention in care [1,32]. Although at later durations of ART, attained is more important than nadir CD4⁺ cell count, it is important to realize that estimated life expectancies are conditional on surviving the first year of ART and this is highly dependent on nadir CD4⁺ cell count [14]. Furthermore, our analysis does not include individuals who never start ART, which will exclude some individuals with the poorest prognosis. Our study supports a previous analysis which showed that patients successfully treated with ART should be eligible for life insurance at affordable premiums [33].

Our study is observational, and therefore associations of CD4⁺ cell count and viral suppression with differences in life expectancy may not be causal. We have not examined whether patients have stopped ART, are poorly adherent or have other risk factors for higher mortality. Failure to attain an adequate CD4⁺ cell count or suppressed viral load may be due to failure of the ART regimen and resistance developing, or due to patients being unable or unwilling to take the treatment [34], but it could also be associated with other lifestyle, behavioural or clinical factors that lead to a higher underlying mortality. HIV-positive populations generally have a higher prevalence of smoking [35], alcohol [36] and illicit drug abuse [37,38], and hepatitis B and C coinfection, which are risk factors for mortality and may be associated with lower attained CD4⁺ cell count and higher viral load [39–41]. Nevertheless, our results indicate that those with CD4⁺ cell count at least 350 cells/ μ l and suppressed viral load have a life expectancy slightly higher than the general population. This could be due to missing deaths or it could be real, as this population is in clinical care and frequently monitored and therefore might receive better management of chronic disease risk factors and earlier diagnosis of other diseases, such as cancer, compared with the general population. In a combined analysis of well controlled HIV-infected adults in the SMART and ESPRIT clinical trials in which ascertainment of death should be less affected by losses to follow-up, SMR estimates for patients with viral suppression and CD4⁺ cell count at least 350 cells/ μ l varied between 1 (0.73–1.34) and 1.57 (1.26–1.94) depending on the criteria used for including follow-up time [9]. SMR estimates were higher for CD4⁺ cell count between 350 and 499 compared with at least 500 cells/ μ l, but CIs overlapped [9]. In our study of patients in usual clinical care, we found no strong evidence of differences in mortality rates between these CD4⁺ cell count categories and therefore did not estimate life expectancy separately.

Conclusion

In the UK, where ART is free and available in an established National Health Service, people living with HIV infection can expect to live as long as the general population if successfully treated. Our study showed that longevity depends on both restoration of CD4⁺ cell count to near normal levels and suppression of the virus to undetectable levels in peripheral blood.

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M.G., M.M. and C.S. did the study design and conception. C.O., S.K., P.H., M.J., A.P., R.G., D.C., F.M., J.W., F.P., M.F., J.A., C.L., M.N. and J.A. collected the data. C.S. coordinated the study. S.J. and T.H. did the data management. M.M. did the statistical analyses and wrote first draft of article with help from M.G. All authors contributed to interpreting the data, critically revising the article and approved the final version.

Conflicts of interest

There are no conflicts of interest.

Appendix

UK CHIC Steering Committee: Jonathan Ainsworth, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Fabiola Martin, Phillip Hay, Teresa Hill, Margaret Johnson, Stephen Kegg, Clifford Leen, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Caroline Sabin (PI), Memory Sachikonye, Achim Schwenk, John Walsh, Alan Winston, Nicky Mackie.

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Ainsworth), Homerton University Hospital NHS Trust, London (Jane Anderson), MRC Clinical Trials Unit, London (David Dunn), South Tees Hospitals NHS Foundation Trust, Middlesbrough (David Chadwick), Public Health England Centre for Infections (PHE CfI), London (Valerie Delpech), Brighton and Sussex University Hospitals NHS Trust, Brighton (Martin Fisher), Chelsea & Westminster Hospital NHS Foundation Trust, London (Brian Gazzard, Mark Nelson), Mortimer Market Centre, University College London Medical School (Richard Gilson), North Bristol NHS Trust, Bristol (Mark Gompels), St George's Healthcare NHS Trust, London (Phillip Hay), Royal Free Hampstead NHS Trust, London (Margaret Johnson), South London Healthcare NHS Trust, London (Stephen Kegg), The Lothian University Hospitals NHS Trust, Edinburgh (Clifford Leen), York Teaching Hospital NHS Foundation Trust (Fabiola Martin), Barts and The London NHS Trust, London (Chloe Orkin), University Hospitals of Leicester NHS Trust (Adrian Palfreeman), King's College Hospital NHS Foundation Trust, London (Frank Post), UK Community Advisory Board (Memory Sachikonye).

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