Age in antiretroviral therapy programmes in South Africa: a retrospective, multicentre, observational cohort study

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Summary

Background As access to antiretroviral therapy (ART) expands, increasing numbers of older patients will start treatment and need specialised long-term care. However, the effect of age in ART programmes in resource-constrained settings is poorly understood. The HIV epidemic is ageing rapidly and South Africa has one of the highest HIV population prevalences worldwide. We explored the effect of age on mortality of patients on ART in South Africa and whether this effect is mediated by baseline immunological status.

Methods In this retrospective cohort analysis, we studied HIV-positive patients aged 16–80 years who started ART for the first time in six large South African cohorts of the International Epidemiologic Databases to Evaluate AIDS-Southern Africa collaboration, in KwaZulu-Natal, Gauteng, and Western Cape (two primary care clinics, three hospitals, and a large rural cohort). The primary outcome was mortality. We ascertained patients' vital status through linkage to the National Population Register. We used inverse probability weighting to correct mortality for loss to follow-up. We estimated mortality using Cox's proportional hazards and competing risks regression. We tested the interaction between baseline CD4 cell count and age.

Findings Between Jan 1, 2004, and Dec 31, 2013, 84 078 eligible adults started ART. Of these, we followed up 83 566 patients for 174 640 patient-years. 8% (1817 of 23 258) of patients aged 16–29 years died compared with 19% (93 of 492) of patients aged 65 years or older. The age adjusted mortality hazard ratio was 2·52 (95% CI 2·01–3·17) for people aged 65 years or older compared with those 16–29 years of age. In patients starting ART with a CD4 count of less than 50 cells per μL, the adjusted mortality hazard ratio was 2·52 (2·04–3·11) for people aged 50 years or older compared with those 16–39 years old. Mortality was highest in patients with CD4 counts of less than 50 cells per μL, and 15% (1103 of 7295) of all patients aged 50 years or older starting ART were in this group. The proportion of patients aged 50 years or older enrolling in ART increased with successive years, from 6% (290 of 4999) in 2004 to 10% (961 of 9657) in 2012–13, comprising 9% of total enrolment (7295 of 83 566). At the end of the study, 6304 (14%) of 44 909 patients still alive and in care were aged 50 years or older.

Interpretation Health services need reorientation towards HIV diagnosis and starting of ART in older individuals. Policies are needed for long-term care of older people with HIV.

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Introduction

The world's population is ageing rapidly. By 2050, WHO estimates that 2 billion individuals 60 years of age or older will be living worldwide, with 80% of these in low-income and middle-income countries.[1] South Africa has the second largest population of older people in sub-Saharan Africa,[2] with this population expected to increase. By 2025, nearly 5·23 million South Africans will be older than 60 years of age.[3] In addition to this rapid ageing in the general population, the HIV epidemic is ageing, and the number of HIV-positive individuals older than 50 years of age in South Africa could triple in the next 30 years.[4] South Africa has the largest antiretroviral therapy (ART) programme worldwide, with an estimated 2·3 million individuals still on treatment in the public sector in March 2013.[5] The country is now facing the challenges of a successful ART programme in the middle of a major demographic transition. As access to treatment expands, increasing numbers of older patients might start ART and need long-term care.

Initiation and retention of older individuals on ART has major public health implications. Older people are not generally targeted for HIV prevention and testing.[6] Health-care workers are less likely to ask about sexual practices and diagnose HIV in older individuals. As a result, older people might start treatment with more advanced HIV disease than do younger people. Additionally, older people are more likely to have comorbidities than are younger patients and they might need more specialised care.[7] HIV has been suggested to mimic the effects of ageing in the immune system, compounded by long-term ART toxic effects and interactions with drugs for other age-related disorders.[8] Poorer outcomes on ART have been reported in older adults than in younger adults.[9]

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Research in context

Evidence before this study

We searched PubMed using the following search terms: ("antiretroviral therapy" OR "antiretroviral treatment") AND "South Africa" AND ("mortality" OR "survival") AND ("aging" OR "ageing" OR "older"). We included studies published in English between Jan 1, 2000, and Dec 31, 2014, on adults aged 16 years or older. Despite the fact that South Africa has the largest antiretroviral therapy (ART) programme worldwide, few studies have explicitly assessed the effect of age on mortality on ART in South Africa. Studies have shown higher mortality in older patients than in younger adults on ART up to 24 months. Older patients had lower loss to follow-up, poorer immunological responses, and better virological responses to ART than did younger patients.

Added value of this study

Our study extends previous findings through to 3 years on ART. Additionally, our study provides new evidence that baseline immunological status modifies the effect of age on mortality on ART. For patients who were healthy, the risk of mortality was not greatly increased by age at ART initiation. However, older patients initiating ART at 50 cells per μL or fewer are a particularly high-risk group, which needs specific clinical and policy considerations.

Implications of all the available evidence

The available evidence suggests that a substantial proportion of older individuals are initiating ART across South Africa and that this proportion has increased in successive years. Targeted programmes are needed to increase voluntary counselling and testing in older individuals. Health-care workers need training to diagnose HIV and to initiate ART early in older patients. In particular, patients aged 50 years and older enrolling on ART with CD4 counts of less than 50 cells per μL are a high-risk group for whom treatment should be expedited. Policies for long-term care of older individuals with HIV are urgently needed.

Little research has been done on age in ART programmes in resource-constrained settings,[10–13] and mortality has been estimated from standard patients' record systems, which miss a high proportion of deaths.[14,15] By use of linkages with the South African vital registration system, the International Epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration is able to correct mortality estimates for loss to follow-up, providing a unique opportunity to explore long-term outcomes for a large number of older individuals starting ART in South Africa since 2004. We investigated the association between age and mortality risk, and whether this effect was modified by immunological status before ART initiation.

Methods

Study design and population

IeDEA-SA is a regional collaboration that combines routine observational data from large ART programmes across southern Africa. This study was a retrospective cohort analysis of data from South African cohorts of IeDEA-SA providing ART services in three of the most populous provinces (KwaZulu-Natal, Gauteng, and Western Cape). Cohorts are predominantly government funded and follow standardised national ART guidelines. Patients are broadly representative of those accessing public sector ART in rural and urban centres.[16]

Data sources

By use of a standardised data transfer format, participating IeDEA-SA cohorts transfer anonymised, routinely collected data to the IeDEA-SA data centre at the University of Cape Town, Cape Town, South Africa. This study included data from six cohorts: Gugulethu and Khayelitsha primary care clinics and Tygerberg hospital in Western Cape province; McCord Hospital and Hlabisa (a large rural cohort of 17 primary health-care clinics) in KwaZulu-Natal; and Themba Lethu (a large urban public hospital) in Gauteng. All HIV-positive adults (16–80 years old) who started ART for the first time between 2004 and 2013 were eligible for inclusion.

Statistical analysis

We cleaned, coded, and analysed data in Stata 13.1. We followed up patients from ART initiation to the earliest of the following: death, loss to follow-up, transfer out, or alive at analysis closure. The primary outcome was mortality. Loss to follow-up and immunological and virological responses were secondary outcomes. We defined loss to follow-up as no contact with the health facility for 6 months.[17] The analysis excluded patients enrolled up to 6 months before database closure to allow the loss to follow-up definition to be met. Because a high proportion of patients lost to follow-up were likely to have died, we used inverse probability weighting to correct mortality for deaths misclassified as loss to follow-up.18 We linked patients lost to follow-up with identification numbers to the National Population Register to confirm vital status and date of death if deceased, and upweighted them to represent all loss to follow-up. Cohorts providing data identified patients who transferred out and the date at which they did so, and their follow-up time was censored on this date. We analysed patients by age group: 16–29 years old and 5 year groups thereafter. We describe summary baseline characteristics (median, IQR, and proportions). We report by age the number and proportion of patients dead, median follow-up times to death, and rates and incidence of mortality. We report the proportions of patients aged 50 years and older at ART initiation and analysis closure by year of enrolment.

	Age (years)									Total
	16–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	≥65	
Patients enrolled	23 258 (28%)	19 372 (23%)	16 231 (19%)	10 616 (13%)	6794 (8%)	4006 (5%)	1991 (2%)	806 (1%)	492 (1%)	83 566 (100%)
Women	18 819 (81%)	12 812 (66%)	9411 (58%)	5975 (56%)	3770 (55%)	2165 (54%)	1040 (52%)	399 (50%)	247 (50%)	54 638 (65%)
CD4 count (cells per μL)	137 (62–210)	120 (152–188)	117 (51–186)	120 (53–186)	124 (59–190)	128 (64–195)	125 (60–190)	130 (66–195)	135 (75–208)	125 (56–192)
Categorical CD4-positive cell count										
0–49	3692 (16%)	3696 (19%)	3182 (20%)	2002 (19%)	1188 (17%)	615 (15%)	326 (16%)	111 (14%)	51 (10%)	14 863 (18%)
50–99	3002 (13%)	2863 (15%)	2514 (15%)	1634 (15%)	1003 (15%)	652 (16%)	300 (15%)	117 (14%)	91 (19%)	12 176 (15%)
100–199	6657 (29%)	5613 (29%)	4646 (29%)	3177 (30%)	2114 (31%)	1210 (30%)	637 (32%)	269 (33%)	143 (29%)	24 466 (29%)
200–349	4030 (17%)	2826 (15%)	2267 (14%)	1471 (14%)	979 (14%)	649 (16%)	278 (14%)	136 (17%)	83 (17%)	12 719 (15%)
350–499	377 (2%)	246 (1%)	232 (1%)	156 (1%)	118 (2%)	66 (2%)	32 (2%)	11 (1%)	10 (2%)	1248 (2%)
≥500	196 (1%)	120 (1%)	118 (1%)	78 (1%)	62 (1%)	40 (1%)	28 (1%)	4 (1%)	9 (2%)	655 (1%)
Missing	5304 (23%)	4008 (21%)	3272 (20%)	2098 (20%)	1330 (20%)	774 (19%)	390 (20%)	158 (20%)	105 (21%)	17 439 (21%)
WHO stage										
1 and 2	6052 (26%)	3802 (20%)	2816 (17%)	1649 (16%)	1033 (15%)	646 (16%)	308 (15%)	128 (16)	91 (19%)	16525 (20%)
3	5560 (24%)	4790 (25%)	3951 (24%)	2617 (25%)	1622 (24%)	935 (23%)	457 (23%)	160 (20)	122 (25%)	20214 (24%)
4	2519 (11%)	2154 (11%)	1744 (11%)	1066 (10%)	674 (10%)	384 (10%)	162 (8%)	77 (10)	42 (9%)	8822 (11%)
Missing	9127 (39%)	8626 (45%)	7720 (48%)	5284 (50%)	3465 (51%)	2041 (51%)	1064 (53%)	441 (55)	237 (48%)	38005 (45%)
Tuberculosis at ART start										
Yes	1725 (7%)	1730 (9%)	1467 (9%)	982 (9%)	633 (9%)	321 (8%)	155 (8%)	64 (8%)	35 (7%)	7112 (9%)
No	8637 (37%)	7109 (37%)	6427 (40%)	4456 (42%)	3043 (45%)	1878 (47%)	999 (50%)	409 (51%)	268 (54%)	33 226 (40%)
Missing	12 896 (55%)	10 533 (54%)	8337 (51%)	5178 (49%)	3118 (46%)	1807 (45%)	837 (42%)	333 (41%)	189 (38%)	43 228 (52%)
Anaemia										
None	3011 (13%)	2925 (15%)	2740 (17%)	1913 (18%)	1286 (19%)	784 (20%)	411 (21%)	134 (17%)	81 (16%)	13 285 (16%)
Mild	4299 (18%)	3613 (19%)	3131 (19%)	2173 (20%)	1447 (21%)	896 (22%)	452 (23%)	173 (21%)	115 (23%)	16 299 (20%)
Moderate	2828 (12%)	2505 (13%)	2133 (13%)	1381 (13%)	945 (14%)	524 (13%)	275 (14%)	125 (16%)	74 (15%)	10790 (13%)
Severe	1051 (5%)	782 (4%)	640 (4%)	422 (4%)	227 (3%)	127 (3%)	49 (2%)	26 (3%)	16 (3%)	3340 (4%)
Missing	12 069 (52%)	9547 (49%)	7587 (47%)	4727 (45%)	2889 (43%)	1675 (42%)	804 (40%)	348 (43%)	206 (42%)	39 852 (48%)
Year of ART initiation										
2004	1419 (6%)	1335 (7%)	1030 (6%)	583 (5%)	342 (5%)	178 (4%)	69 (3%)	27 (3%)	16 (3%)	4999 (6%)
2005	1976 (9%)	1745 (9%)	1339 (8%)	799 (8%)	527 (8%)	242 (6%)	108 (5%)	39 (5%)	18 (4%)	6793 (8%)
2006	2291 (10%)	2181 (11%)	1629 (10%)	1162 (11%)	623 (9%)	375 (9%)	167 (8%)	59 (7%)	34 (7%)	8521 (10%)
2007	2265 (10%)	2129 (11%)	1737 (11%)	1166 (11%)	714 (11%)	378 (9%)	202 (10%)	67 (8%)	38 (8%)	8696 (10%)
2008	2751 (12%)	2347 (12%)	1990 (12%)	1293 (12%)	841 (12%)	506 (13%)	244 (12%)	94 (12%)	63 (13%)	10 129 (12%)
2009	2892 (12%)	2615 (14%)	2169 (13%)	1473 (14%)	997 (15%)	588 (15%)	289 (15%)	121 (15%)	57 (12%)	11 201 (13%)
2010	3605 (16%)	2664 (14%)	2322 (14%)	1440 (14%)	938 (14%)	589 (15%)	319 (16%)	127 (16%)	84 (17%)	12 088 (14%)
2011	3304 (14%)	2346 (12%)	2148 (13%)	1492 (14%)	956 (14%)	639 (16%)	347 (17%)	150 (19%)	100 (20%)	11 482 (14%)
2012–13	2755 (12%)	2010 (10%)	1867 (12%)	1208 (11%)	856 (13%)	511 (13%)	246 (12%)	122 (15%)	82 (17%)	9657 (12%)
Weight (kg)	60 (52–69)	61 (54–70)	62 (55–71)	62 (54–72)	62 (54–72)	62 (54–71)	62 (54–72)	61 (53–71)	60 (51–70)	61 (54–70)
Outcome at analysis closure										
Deaths	1817 (8%)	1746 (9%)	1556 (10%)	1124 (11%)	767 (11%)	515 (13%)	275 (14%)	136 (17%)	93 (19%)	8029 (10%)
Transferred out	2749 (12%)	2128 (11%)	1672 (10%)	1060 (10%)	667 (10%)	385 (10%)	187 (9%)	73 (9%)	40 (8%)	8961 (11%)
Lost to follow-up	6828 (29%)	5229 (27%)	4068 (25%)	2536 (24%)	1500 (22%)	815 (20%)	417 (21%)	186 (23%)	88 (18%)	21667 (26%)
Alive	11 864 (51%)	10 269 (53%)	8935 (55%)	5896 (56%)	3860 (57%)	2291 (57%)	1112 (56%)	411 (51%)	271 (55%)	44 909 (54%)
Mortality rate per 100 person-years	3·1	3·2	3·6	4·0	4·5	5·6	6·6	9·4	11·4	3·7
Median days to death	749	863	795	799	746	700	606	473	420	777

Data are n (%) or median (IQR) unless otherwise stated. ART=antiretroviral therapy.

Table 1: **Baseline characteristics, year of ART initiation, patient outcomes, and mortality rates, by age at enrolment**

We used Cox's proportional hazards models to assess crude and adjusted associations between patients' characteristics and outcomes. We adjusted models for baseline characteristics (sex, CD4 cell count, WHO stage, haemoglobin, tuberculosis, weight, and site of ART initiation) and stratified them by duration on ART.

Assuming that data were likely to be missing at random, we used multiple imputation[19] with chained equation methods[20] to impute missing baseline covariates. We multiply imputed ten times CD4 cell count (baseline, 12 months, and 24 months), baseline WHO stage, weight, haemoglobin, and tuberculosis (yes or no). We explored immunological response by reporting and graphing CD4 cell counts at baseline and 12 months, 24 months, and 36 months on ART. We reported the percentage of virally suppressed (viral load measurement of less than 400 copies per mL) patients at 12 months, 24 months, and 36 months. We assessed whether the effect of age on mortality risk was modified by baseline CD4 cell count by recategorising age (16–39 years, 40–49 years, and 50 years and older) and CD4 counts (less than 50 cells per µL, 50–199 cells per µL, and 200 cells per µL or higher). We included their interaction in the models and graphed the hazard ratios (HRs) of this interaction. We compared estimates of mortality and loss to follow-up with Kaplan-Meier and competing risks methods, and explored possible heterogeneity between cohorts by comparing median ages, numbers (and proportions) of patients aged 50 years and older at ART initiation and analysis closure, and crude HRs for the effect of age on mortality, by cohort.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2004, and Dec 31, 2013, 84078 eligible adults started ART in the six cohorts. Of these, we excluded 512 because of missing or invalid dates (504 [1%]) and unknown sex (eight [<1%]). The analysis

	Overall		0–12 months	12–24 months	24–36 months
	HR	aHR	aHR	aHR	aHR
Age (years)					
16–29	1	1	1	1	1
30–34	1·06 (0·99–1·14)	1·03 (0·96–1·10)	1·05 (0·90–1·22)	0·99 (0·73–1·35)	0·83 (0·56–1·23)
35–39	1·16 (1·08–1·24)	1·12 (1·04–1·20)	1·14 (0·99–1·32)	1·11 (0·82–1·50)	0·83 (0·57–1·22)
40–44	1·29 (1·20–1·40)	1·24 (1·14–1·34)	1·26 (1·09–1·46)	1·14 (0·84–1·55)	0·78 (0·53–1·17)
45–49	1·45 (1·33–1·58)	1·35 (1·23–1·48)	1·37 (1·17–1·60)	1·39 (1·01–1·91)	0·87 (0·57–1·32)
50–54	1·73 (1. 57–1·92)	1·65 (1·48–1·84)	1·52 (1·28–1·80)	1·63 (1·16–2·27)	1·26 (0·82–1·93)
55–59	1·94 (1·70–2·20)	1·86 (1·63–2·14)	1·89 (1·57–2·27)	1·85 (1·30–2·66)	1·87 (1·20–2·92)
60–64	2·63 (2·19–3·16)	2·49 (2·04–3·06)	2·04 (1·63–2·54)	1·77 (1·11–2·82)	2·44 (1·45–4·10)
≥65	3·00 (2·43–3·70)	2·52 (2·01–3·17)	2·79 (2·21–3·53)	3·21 (2·04–5·06)	2·06 (1·07–3·98)
Men	1·62 (1·55–1·70)	1·40 (1·33–1·48)	1·28 (1·19–1·37)	1·38 (1·20–1·59)	1·74 (1·45–2·10)
CD4 count (cells per µL)					
<50	1	1	1	1	1
50–99	0·64 (0·60–0·68)	0·71 (0·65–0·78)	0·60 (0·55–0·65)	0·82 (0·69–0·97)	0·91 (0·72–1·17)
100–199	0·39 (0·36–0·41)	0·54 (0·48–0·59)	0·40 (0·37–0·44)	0·61 (0·52–0·72)	0·85 (0·68–1·06)
200–349	0·24 (0·22–0·26)	0·38 (0·33–0·43)	0·30 (0·26–0·35)	0·53 (0·41–0·68)	0·60 (0·42–0·86)
350–499	0·34 (0·27–0·44)	0·52 (0·41–0·65)	0·43 (0·31–0·59)	0·64 (0·34–1·22)	1·25 (0·58–2·70)
≥500	0·26 (0·18–0·37)	0·44 (0·30–0·63)	0·39 (0·25–0·62)	0·40 (0·13–1·26)	1·60 (0·59–4·31)
WHO stage					
1 and 2	1	1	1	1	1
3	2·40 (2·18–2·65)	1·64 (1·48–1·82)	1·61 (1·34–1·93)	1·70 (1·34–2·16)	1·53 (1·12–2·08)
4	4·06 (3·66–4·51)	2·37 (2·09–2·70)	2·42 (1·98–2·97)	2·15 (1·69–2·75)	2·14 (1·52–3·02)
Anaemia					
None	1	1	1	1	1
Mild	1·76 (1·64–1·89)	1·37 (1·25–1·50)	1·51 (1·31–1·75)	1·37 (1·10–1·71)	1·33 (1·00–1·76)
Moderate	3·10 (2·87–3·35)	1·99 (1·82–2·17)	2·40 (2·05–2·81)	1·77 (1·41–2·22)	1·57 (1·14–2·15)
Severe	4·72 (4·00–5·56)	2·92 (2·60–3·28)	3·89 (3·35–4·52)	2·03 (1·46–2·84)	1·66 (1·04–2·64)
Tuberculosis at enrolment	1·53 (1·40–1·65)	0·82 (0·76–0·90)	0·81 (0·73–0·91)	0·83 (0·66–1·04)	0·92 (0·72–1·18)
Weight (kg)	0·96 (0·96–0·96)	0·98 (0·97–0·98)	0·97 (0·97–0·98)	0·98 (0·98–0·99)	0·99 (0·99–0·99)

Mortality corrected via linkage to the National Population Register and adjusted for baseline characteristics and site of antiretroviral therapy initiation. HR=hazard ratio. aHR=adjusted hazard ratio.

Table 2: **Crude and adjusted mortality after multiple imputation, overall, and by duration on antiretroviral therapy**

therefore included 83 566 patients followed up for 174 640 person-years. Median follow-up was 2·13 person-years (IQR 0·77–4·13). The proportion of patients enrolled in successive age groups decreased from 16–29 year olds to those aged 65 years and older (table 1). Most patients were women, especially in the young age groups. Median CD4 cell counts were similar in patients aged 16–29 years and 65 years and older, as were the proportions of patients in WHO stages 3 and 4.

1817 (8%) of 23 258 patients aged 16–29 years died compared with 93 (19%) of 492 aged 65 years and older; the proportion of patients lost to follow-up was higher in younger than in older patients (table 1). Median duration of follow-up decreased with increasing age, and the overall mortality rate increased. At 12 months, the cumulative incidence of mortality was 6·9% (95% CI 6·7–7·1), at 24 months, 9·2% (8·9–9·4), and 36 months, 10·8% (10·6–11·1), with slightly lower estimates derived from competing risks analysis than from Kaplan-Meier estimates (appendix). The proportion of patients aged 50 years and older at ART initiation was 9% (7295 of 83 566), and increased from 6% (290 of 4999) in 2004 to 10% (961 of 9657) in 2012–13 (appendix). Within cohorts, this proportion ranged from 6% (1473 of 23 713) in Khayelitsha to 11% (2167 of 19 946) in Hlabisa. At analysis closure, 14% (6304 of 44 909) of patients alive and in care were aged 50 years or older, ranging from 10% (1479 of 14 096) in Khayelitsha to 16% in the large cohorts in Themba Lethu (1850 of 11 433) and Hlabisa (2253 of 19 946).

With univariate analysis, we noted a dose response between increasing age and hazard of death (table 2). The crude hazard relative to that in people aged 16–29 years was slightly higher in those aged 35–39 years and three times higher in patients aged 65 years and older (table 2). These associations were attenuated but persisted in a multivariable analysis adjusted for baseline characteristics (table 2). The effect of age on mortality persisted with increasing duration on ART, but with less precise estimates. Other baseline characteristics that increased adjusted risk of mortality were being male, having WHO stages 3 or 4 compared with 1 and 2, and

See Online for appendix

	Age (years)									Total
	16–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	≥65	
Patients enrolled	23 258 (28%)	19 372 (23%)	16 231 (19%)	10 616 (13%)	6794 (8%)	4006 (5%)	1991 (2%)	806 (1%)	492 (1%)	83 566 (100%)
CD4-positive cell count (cells per μL)										
Baseline										
Cell count	137 (62 to 201)	120 (52 to 188)	117 (51 to 186)	120 (53 to 186)	124 (59 to 190)	128 (64 to 195)	125 (60 to 190)	130 (67 to 195)	135 (75 to 208)	125 (56 to 192)
12 months on ART										
Cell count	324 (223 to 449)	294 (201 to 408)	274 (189 to 384)	273 (186 to 381)	273 (187 to 384)	261 (177 to 373)	263 (177 to 366)	266 (184 to 369)	240 (167 to 336)	291 (198 to 405)
Cell count increase from baseline (cells per μL)	194 (115 to 293)	173 (100 to 263)	156 (88 to 245)	155 (85 to 241)	147 (75 to 232)	138 (72 to 222)	127 (66 to 221)	120 (57 to 219)	102 (50 to 180)	167 (92 to 159)
24 months on ART										
Cell count	403 (286 to 539)	376 (269 to 503)	350 (249 to 472)	349 (247 to 474)	343 (241 to 468)	330 (227 to 451)	323 (219 to 439)	322 (214 to 441)	298 (217 to 436)	367 (258 to 497)
Cell count increase from 12 months	87 (5 to 176)	83 (13 to 159)	78 (12 to 152)	75 (9 to 149)	70 (7 to 149)	68 (5 to 135)	63 (6 to 122)	52 (–6 to 131)	64 (4 to 170)	79 (9 to 157)
36 months on ART										
Cell count	447 (313 to 591)	426 (303 to 563)	402 (290 to 528)	397 (280 to 536)	397 (286 to 544)	379 (273 to 516)	354 (245 to 477)	333 (247 to 460)	328 (260 to 448)	415 (295 to 555)
Cell count increase from 24 months	49 (–38 to 141)	52 (–25 to 136)	53 (–17 to 127)	56 (–18 to 126)	57 (–8 to 135)	46 (–10 to 123)	52 (–19 to 115)	37 (–24 to 80)	30 (–1 to 122)	52 (–23 to 132)
Virological response										
12 months										
Patients with viral load data	8196 (35%)	7868 (41%)	6451 (40%)	4149 (39%)	2573 (38%)	1404 (35%)	660 (33%)	250 (31%)	104 (21%)	31 655 (38%)
Patients suppressed*	6855 (84%)	6782 (86%)	5612 (87%)	3658 (88%)	2227 (87%)	1232 (88%)	583 (88%)	220 (88%)	92 (88%)	27 261 (86%)
24 months										
Patients with viral load data	5749 (25%)	5710 (29%)	4585 (28%)	2863 (27%)	1706 (25%)	950 (24%)	433 (22%)	164 (20%)	66 (13%)	22 226 (27%)
Patients suppressed*	4715 (82%)	4914 (86%)	3967 (87%)	2494 (87%)	1500 (88%)	817 (86%)	381 (88%)	144 (88%)	57 (86%)	18 989 (85%)
36 months										
Patients with viral load data	4064 (17%)	4127 (21%)	3250 (20%)	2030 (19%)	1196 (18%)	653 (16%)	264 (13%)	90 (11%)	30 (6%)	15 704 (19%)
Patients suppressed*	3269 (80%)	3514 (85%)	2804 (86%)	1743 (86%)	1054 (88%)	557 (85%)	223 (84%)	79 (88%)	26 (87%)	13 269 (84%)

Data are n (%) or median (IQR). *Percentages are of the number of patients with viral loads.

Table 3: **Immunological and virological responses by age and duration on antiretroviral therapy**

having any level of anaemia compared with none. Relative to mortality in patients starting ART at CD4 counts of less than 50 cells per µL, the hazard of death was lowest in patients enrolling at 200–349 cells per µL. Having tuberculosis at ART initiation increased the risk of death in crude but not multivariable analysis (table 2). In a sensitivity analysis limited to cohorts that collected identification numbers, point estimates were similar, but less precise. In an analysis to explore heterogeneity, point estimates for the effect of age on hazard of mortality were similar across all cohorts (appendix).

Although we noted no difference in baseline median CD4 cell counts between the youngest and oldest age groups, immunological responses on ART were clearly age related, with smaller gains in CD4 cell counts at older ages than at younger ages (table 3). Differences in immunological responses noted over time seemed to be driven by responses in the first year on treatment (figure). In subsequent years, immunological response had the same age pattern as in the first year. Although age increased the risk of mortality, this effect was modified by baseline immunological status and was more pronounced at lower baseline CD4 cell counts than at higher counts (table 4). Overall, 1103 (15%) of 7295 patients aged 50 years or older started ART with CD4 counts of less than 50 cells per µL, ranging from 9% (205 of 2167) in Hlabisa to 25% (150 of 608) in McCord hospital.

Of patients with viral load measures, virological suppression was good across all ages, maintained through to 36 months on treatment (table 3). With crude and multivariable analysis, all patients aged 30–60 years at enrolment had a lower hazard of loss to follow-up than did the youngest patients: adjusted HR 0·82 (95% CI 0·74–0·91) for those aged 55–59 years compared with 16–29 years (appendix). The cumulative incidence of loss to follow-up at 12 months on ART was 12·2% (95% CI 12·0–12·5), at 24 months was 18·9% (18·3–18·9), and at 36 months was 24·3% (23·9–24·6), with slightly lower estimates from competing risks analysis than from Kaplan-Meier estimates.

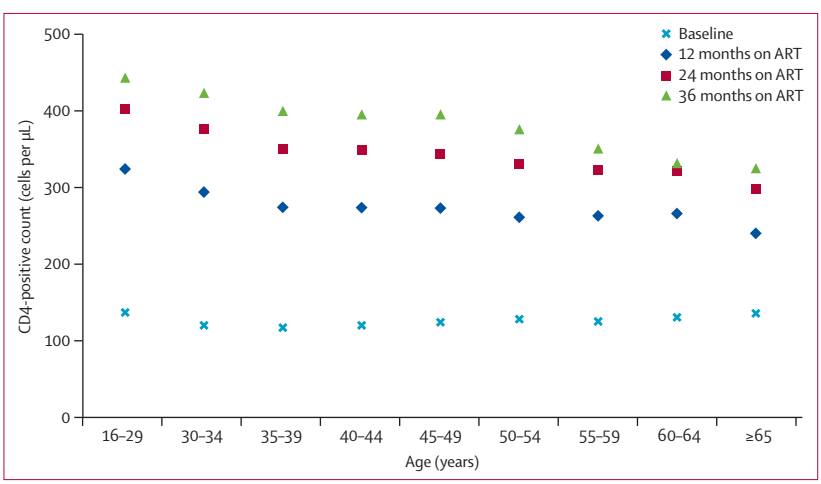

Figure: **Median CD4 cell count by age and duration on ART**
ART=antiretroviral therapy.

	<50 cells per µL	50–199 cells per µL	≥200 cells per µL
16–39 years	1	1	1
40–49 years	1·49 (1·24–1·80)	1·25 (1·15–1·36)	1·14 (1·03–1·27)
≥50 years	2·52 (2·04–3·11)	1·79 (1·62–1·98)	1·54 (1·33–1·78)

Data are hazard ratios (95% CI).

Table 4: **Interaction between effects of age and baseline CD4 on mortality**

Discussion

We noted increasing proportions of patients aged 50 years and older initiating ART in successive years. The hazard of death increased with baseline age, whereas loss to follow-up did not. Although baseline CD4 cell counts were similar across all age groups, the effect of age on mortality was modified by baseline immunological status and was more pronounced at low CD4 cell counts. Early immunological responses were diminished in older patients, but virological responses were good at all ages.

Concern is growing about the absence of data for HIV and ART in older adults in Africa.[6,7,21] Our study provides new evidence that a substantial proportion of older individuals are initiating ART across South Africa and that this proportion is increasing with each successive year. Despite the absence of a programme targeting older individuals for HIV testing and treatment, nearly 10% of all new patients in our study were aged 50 years and older, similar to findings from Malawi,[22] Uganda,[23] and nine countries in sub-Saharan Africa.[13] These findings represent a substantial and poorly understood burden of care in years to come. Initiation of ART in older individuals raises several important issues. People who are aged 50 years and older are less likely to have ever tested for HIV than are those aged 15–49 years, and older people are less likely than younger ones are to have used a condom during recent sex.[24] Despite these factors, health-care workers are less likely to consider an HIV diagnosis in older patients than in young patients.[25] Additionally, compounding the body's natural ageing processes, older people have more non-communicable diseases than do younger individuals, with possible interactions between other chronic drugs and ART.[8] Health services need to target this neglected group for HIV testing and prevention. Health-care workers need training to diagnose HIV in older individuals and initiate and manage them on ART to ensure good outcomes on treatment.

In particular, our results suggest that older patients starting ART with CD4 counts of less than 50 cells per µL should be recognised as a high-risk group. Our findings show a dose response between increasing age at ART initiation and hazard of mortality, and the association between baseline CD4 cell count and

mortality is well established.[9,26] Poorer immunological responses in older patients than in younger patients in the first year on ART have been documented in west Africa.[11] Our study extends these findings through to 3 years on treatment. Additionally, to our knowledge, this study is the first to report that baseline immunological status modifies the effect of age on mortality, identifying a group of patients needing additional attention in ART programmes. Although the risk of mortality increased with age, the effect of age was strongest at the lowest baseline CD4 cell counts (ie, in patients who were healthy, the risk of mortality was not greatly increased by age at ART initiation). In patients with severely compromised immune systems, age had a strong effect on mortality risk. Overall, 15% of all older patients started treatment with CD4 counts of less than 50 cells per μL, and in one cohort, this high-risk group consisted of 25% of patients. At the programme level, older individuals starting ART at low CD4 cell counts should be prioritised as a high-risk category, with specific clinical and policy considerations.

The increasing proportion of older patients starting ART during successive years of enrolment shows the urgent need for more epidemiological data for HIV in older adults than currently exists. HIV prevalence is not generally measured in older individuals. Prevalence estimates are largely based on antenatal surveys limited to women of reproductive age and Demographic and Health Surveys restricted to adults aged 50 years and younger. Extending the age limit of such surveys, the 2012 South African household survey reported a 4% prevalence in individuals aged 60 years and older.[27] By contrast, investigators of community-level rural surveys have reported prevalences in individuals between 60 years and 70 years of age, ranging from 10·3% to 19·8% in Limpopo,[28] and 4·5% to 10% in KwaZulu-Natal.[29] Although these areas are particularly severely affected by HIV, with higher prevalences than national averages, older adults might be under-represented in existing household surveys. Data are needed for duration of HIV infection in older individuals before ART initiation. Older people could have been infected a long time ago and might be a group of long-term survivors with particular features needing research. In our study, older patients did not have more advanced HIV disease at ART initiation than did younger patients. This finding suggests that at least some older patients were recently infected.[28] Epidemiological measures need to be urgently extended beyond 50 years of age, and accurate data on HIV in older individuals are needed to plan for their care.

This study is strengthened by large numbers of patients, including more than 7000 patients older than 50 years of age at ART initiation, and good mortality ascertainment through linkage to the National Population Register. Identification of a particular high-risk group in older individuals provides important new clinical and policy information. A further strength is consistency of findings across cohorts, increasing confidence in overall estimates. However, interpretation of these results has several limitations. The data come from many ART programmes, and a substantial amount of data is missing, such as baseline CD4 cell counts, which we addressed with multiple imputation. A further limitation is absence of data for cause of death. Findings from previous studies have suggested that older adults might have higher adherence to ART than do younger adults, a factor that could affect outcomes.[30] However, data on adherence were not routinely collected or included in these datasets, and we were unable to explore this possible association. Our findings are likely to be generalisable to the national ART programme and other settings in sub-Saharan Africa, but further research is needed in different contexts.

Age is routinely reported as a demographic variable, but its specific effect on HIV-related mortality has received surprisingly little attention in African ART programmes. Findings from our study suggest that 10 years into the national ART programme, the time has come to address the needs of older adults with HIV in South Africa. Prevention and testing campaigns need to target older adults. Health-care workers need training in diagnosis of HIV in older individuals and initiation and management of them on ART to ensure good outcomes on treatment. The risks of comorbidities and interactions between ART and other drugs in older patients need to be quantified. Policies for long-term care of older individuals with HIV are urgently needed.

Contributors

MC searched the literature, designed the study, analysed the data, generated the tables and figures, interpreted the results, wrote all drafts, and finalised the report. LFJ and MS provided statistical support. FT, MM, RW, HP, JG, and KS managed the cohort and transferred routinely collected data. LM was the senior author. LM, ME, and AB commented on the study design, analyses, and report. All authors reviewed the final report and approved the version to be published.

Declaration of interests

We declare no competing interests.

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