Mutevedzi, PC; Lessells, RJ; Rodger, AJ; Newell, ML (2011) Association of Age with Mortality and Virological and Immunological Response to Antiretroviral Therapy in Rural South African Adults. PLoS One, 6 (7). ISSN 1932-6203 DOI: 10.1371/journal.pone.0021795

Downloaded from: http://researchonline.lshtm.ac.uk/365/

DOI: 10.1371/journal.pone.0021795

Usage Guidelines

Please refer to usage guidelines at http://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by/2.5/
Association of Age with Mortality and Virological and Immunological Response to Antiretroviral Therapy in Rural South African Adults

Portia C. Mutevedzi¹,²*, Richard J. Lessells¹,³, Alison J. Rodger², Marie-Louise Newell¹,⁴

¹Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa, ²Department of Infection and Population Health, University College London, London, United Kingdom, ³Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom, ⁴Institute of Child Health, University College London, London, United Kingdom

Abstract

Objective: To assess whether treatment outcomes vary with age for adults receiving antiretroviral therapy (ART) in a large rural HIV treatment cohort.

Design: Retrospective cohort analysis using data from a public HIV Treatment & Care Programme.

Methods: Adults initiating ART 1st August 2004 - 31st October 2009 were stratified by age at initiation: young adults (16–24 years) mid-age adults (25–49 years) and older (≥50 years) adults. Kaplan-Meier survival analysis was used to estimate mortality rates and age and person-time stratified Cox regression to determine factors associated with mortality. Changes in CD4 cell counts were quantified using a piecewise linear model based on follow-up CD4 cell counts measured at six-monthly time points.

Results: 8846 adults were included, 808 (9.1%) young adults; 7119 (80.5%) mid-age adults and 919 (10.4%) older adults, with 997 deaths over 14,778 person-years of follow-up. Adjusting for baseline characteristics, older adults had 32% excess mortality ($p = 0.004$) compared to those aged 25–49 years. Overall mortality rates (MR) per 100 person-years were 6.18 (95% CI 4.90–7.78); 6.55 (95% CI 6.11–7.02) and 8.69 (95% CI 7.34–10.28) for young, mid-age and older adults respectively. In the first year on ART, for older compared to both young and mid-aged adults, MR per 100 person-years were significantly higher; 0–3 months (MR: 27.1 vs 17.17 and 21.36) and 3–12 months (MR: 9.5 vs 4.02 and 6.02) respectively. CD4 count reconstitution was lower, despite better virological response in the older adults. There were no significant differences in MR after 1 year of ART. Baseline markers of advanced disease were independently associated with very early mortality (0–3 months) whilst immunological and virological responses were associated with mortality after 12 months.

Conclusions: Early ART initiation and improving clinical care of older adults are required to reduce high early mortality and enhance immunologic recovery, particularly in the initial phases of ART.

Introduction

Older adults (≥50 years old) comprise a significant proportion of people enrolling in HIV treatment programmes in sub-Saharan Africa yet outcomes after initiation of antiretroviral therapy (ART) for this group have not been well described. Older adults have generally been neglected in addressing the global HIV epidemic [1]. Indeed, reporting mechanisms and estimates of epidemiological trends usually only encompass adults aged 15–49 [2]. UNAIDS estimated that globally there were 2.8 million adults aged 50 years and older living with HIV in 2005 [3]. Data from our surveillance programme in rural KwaZulu-Natal estimates overall HIV prevalence rate at 9.5% and incidence of 1% in adults aged 50 years and older [4]. In a verbal autopsy study in rural Kenya, HIV was the cause of death in 27% of people aged 50 years and older and was the leading cause of death up to the age of 70 years [5].

Age is a major determinant of mortality for many diseases in the absence of HIV and ART [6]. In the pre-antiretroviral therapy (ART) era, data from sub-Saharan Africa showed that older age at seroconversion was associated with more rapid progression to death [7,8,9,10]. Since the introduction of ART, there have been conflicting data on outcomes for older individuals. Assessing age as a continuous variable, two studies have suggested an association...
between increasing age and higher mortality on ART [11,12].
Two studies analysing age as a categorical variable have reported
significantly higher mortality for individuals aged >50 years: the
ART-LINC cohort in an analysis of 7100 patients from 10 sites
reported a two-fold increased risk in overall mortality for those
≥50 years compared to 16–29 year olds [13]; while in the South
African Free State programme there was 38% increased risk of
mortality for adults >50 years compared to 20–29 year olds,
although the mortality also included people dying before ART
initiation [14]. Other studies including a 7 year cohort in Senegal
have reported no clear association between age and mortality on
ART [15,16,17,18,19]. Comparison across studies is complicated
by the use of different age categories. Moreover these studies have
included age as an explanatory variable rather than explicitly
assessing mortality within and between younger and older ages.
ART outcomes including mortality, immunological and virological
response may potentially be influenced by age [20,21] hence it is
important to understand treatment outcomes to inform on
appropriate HIV management in older adults. We aim to
explicitly assess how mortality rates following ART initiation
compare between older and younger adults and the factors
associated with mortality in each age category using data from a
large rural HIV Treatment and Care cohort and to quantify
immunological and virological responses in different age groups.

Methods

Ethics statement

Written informed consent was obtained from all participants in the
programme to allow use of anonymised routine clinical data in
research. Ethical approval for retrospective analysis of these data
was obtained from the Biomedical Research Ethics Committee of
the University of KwaZulu-Natal (BE066/07) and the Research
Office of the KwaZulu-Natal Department of Health.

Hlabisa HIV Treatment and Care Programme. The
Hlabisa HIV Treatment & Care Programme is a partnership
between the local Department of Health (DoH) and the Africa
Centre for Health and Population Studies (www.africacentre.ac.
za). The details of the programme have been previously described
[22,23].
The programme adheres to the national antiretroviral treatment
guidelines which at the time of study recommended initiation of
ART for adults with WHO stage IV disease or CD4 cell count
≤200 cells/mm³ [24]. Co-trimoxazole was indicated for all
individuals with CD4 count ≤200 cells/mm³ or WHO stage ≤3/4.
First-line ART consisted of stavudine (d4T), lamivudine (3TC), and
either efavirenz (EFV) or nevirapine (NVP). ART was initiated at
primary health care (PHC) clinics (or at Hlabisa district hospital) by
a physician; monitoring and ART dispensing was subsequently
performed by nurses and counsellors. CD4 cell count and HIV viral
load were measured every 6 months on ART.

Data acquisition. Clinical information at baseline and at
monthly clinical visits after initiation of ART is transferred from
standardised clinic records to a centralised Microsoft® Access
database. A comprehensive tracking service operates whereby
patients who are more than one week late for their clinic visit are
contacted by telephone and, if necessary, visited at home by a
tracker nurse. Information pertaining to death after initiation of
ART is therefore obtained either by the clinic staff or tracker team
through communication with family members, other clinic staff, or
hospital staff. Cause of death is recorded if known but not
systematically sought within the routine programme. Laboratory
results (CD4 cell count and HIV viral load) are regularly updated from
the National Health Laboratory Service (NHLS) laboratory
at a district hospital (Hlabisa Hospital). CD4 counts were analysed
using the Beckman Coulter EPICS® XL flow cytometer (Beckman
Coulter, Inc.). Viral load was measured at a provincial laboratory
using the NucliSens EasyQ® HIV-1 assay (bioMérieux), with a
lower detection limit of 25 copies/ml.

Data analysis. Analysis included all adults (≥16 years) who initiated
ART between 1st August 2004 and 31st October 2009,
excluding patients on ART who transferred into the programme
from elsewhere. Analysis was stratified by age at initiation (<50
years and ≥50 years), a classification which ensured consistency
with previous reports [21]. The <50 years age group was further
stratified into 16–24 years and 25–49 years to assess for
heterogeneity in overall outcomes and baseline descriptions. We
assessed differences between the three groups in baseline clinical
characteristics using the non-parametric equality-of-medians test
for continuous variables and proportions test for categorical
variables. Estimated glomerular filtration rate (eGFR) was
calculated using the 4-variable Modification of Diet in Renal
Disease (4-v MDRD) equation, without the ethnicity correction
factor, as validated in a South African population [25,26].

Kaplan-Meier survival analysis was used to assess and compare
mortality between and within age strata. Data was censored at earliest
date of death, date of loss to follow-up, date of transfer out of
programme, or 22nd April 2010. Loss to follow-up was defined as
three consecutive months without a clinic visit. To ascertain the
independent influence of age on overall mortality, a Cox regression
model adjusted for all significantly different baseline factors
(P<0.05) was used to assess mortality hazard difference by age strata. The two
bottom age strata (young and mid-age groups) were combined in the
analysis for determination of mortality risk factors because there were
no statistically significant mortality outcome differences between the
two groups. This is also consistent with previous analysis that have
assessed those aged below 50 years as one group in comparison to
those aged 50 years and above [27,28,29,30]. Stratified Cox regression with time split at 3
and 12 months post-ART initiation was used to determine risk factors for mortality in the periods 0–3
months (very early mortality), 3–12 months (early mortality), and
>12 months post-ART initiation. For the two periods in the first
year, analysis was further stratified by age to establish differences in
mortality predictors between old and young patients. For all Cox
models, variables that were associated with mortality at 15% significance level were individually included into the model and
model goodness-of fit assessed. Validity of the proportional hazards
assumption was tested using the score test based on scaled Schoenfeld
residuals [31]. All results are reported at 5% significance level.

Changes in CD4 cell counts in the 24 months following ART
initiation were quantified using a piecewise linear model based on
follow-up CD4 cell counts measured at six-monthly time points ±
three months. For 909 and 504 patients with missing CD4 counts
at 6 months and 12 months respectively the value was interpolated
from their CD4 cell counts immediately before and after that time
point. Of the 2977 patients alive and active 12 months post ART
initiation, 2187 patients (73.5%) had a recorded CD4 count.

Virological response at one year was based on viral load
measured between 6 and 15 months after ART initiation. The
effect of suboptimal virological response (defined as viral load
≥400 copies/ml) on mortality after the first year of ART was
quantified in a Cox regression model adjusted for baseline
variables and follow-up CD4 cell counts. For both viral loads
and CD4 counts, where more than one measurement was
available within the specified time period, the one closest to that
time point was used.

Sensitivity analysis. To account for the effect of missing
baseline and follow-up explanatory data, we assessed for any
differences in mortality in those with missing observations compared to those with recorded observations. Where those with missing data had significantly different mortality rates, we maintained a category of the missing group within the respective variable in both the univariable and multivariable models exploring factors associated with mortality. This adjusted for any overestimation of the effect of measured/recorded variables on mortality in the absence of those with unmeasured/missing variables. To assess for the extent of loss to follow up bias, we conducted sensitivity analyses where patients lost were considered dead. All analyses were performed with STATA version 11.0 (College Station, Texas, USA).

Results

Patient characteristics

Between 1st August 2004 and 31st October 2009, 8846 adults initiated ART in the programme. Of these, 808 (9.1%) were aged 16–24 years, 7119 (80.5%) were aged 25–49 years and 919 (10.4%) were ≥50 years at time of ART initiation (range 16–83 years). Overall median baseline CD4 cell count was 119 cells/μl prior to ART initiation and the highest median CD4 count was amongst those aged 16–24 years (Table 1).

Mortality

There were 997 deaths in 14,778 person-years of follow-up (72 in adults aged 16–24 years; 790 in adults 25–49 years and 135 in adults ≥50 years at ART initiation). The overall mortality rate was 6.75 per 100 person-years (95% confidence interval [CI] 6.34–7.18), significantly higher for ≥50 year old adults (8.69 per 100 person-years, 95% CI 7.34–10.23) than younger adults (6.18 per 100 person-years, 95% CI 4.90–7.70 and 6.53 per 100 person-years, 95% CI 6.11–7.02 in those age 16–24 years and 25–49 years old respectively). Overall, controlling for baseline differences (sex, WHO disease stage, baseline CD4 cell count, haemoglobin, weight, eGFR, education and employment) there was 32% excess mortality risk in patients aged ≥50 years (aHR 1.32, 95% CI 1.09–1.60, P=0.004) compared to those aged 25–49. There were no significant differences in either overall mortality or time stratified mortality rates between those initiating aged 16–24 and those aged 25–49 (Table 2).

In all age groups, the majority of deaths (769 deaths, 77.1%) occurred in the first year after ART initiation, with mortality particularly high in the first three months after ART initiation (449 deaths, 45.0%). Figure 1A (Kaplan-Meier curve) illustrates mortality differences between the two age groups. Early mortality rates were significantly higher for older adults (≥50 years) but there was no significant mortality difference after 12 months (Table 2).

Immunological response

Despite baseline CD4 cell count being higher for older adults; their median CD4 cell count post-ART initiation was lower than for both groups of younger adults at each time point (Figure 2A). Overall 16.6% had a poor immunological response (failed to achieve a CD4 count increase of ≥50 CD4 cells) in the first 6 months of therapy with the largest proportion being in those aged

Table 1. Baseline characteristics for individuals initiated on ART August 2004 - October 2009 (n = 8846), stratified by age at ART initiation.

| Variable | 16–24 years | | | 25–49 years | | | 50 years | | |
|----------|-------------|------------------|-------------------|-------------|------------------|-------------------|-------------|------------------|-------------------|
| | N | % or median (IQR) (95% CI) | | N | % or median (IQR) (95% CI) | | N | % or median (IQR) (95% CI) | |
| Age | | | | | | | | | |
| 16-24 | 808 | 22 (21–24) | | 7119 | 35 (30–40) | | 919 | 54 (51–58) | |
| 25–49 | 50 | 13.24 | | 10.90–15.58 | | 50 | 13.24 | | 10.90–15.58 | |
| 50+ | 328 | 40.59 | | 37.21–43.98 | | 3435 | 48.25 | | 47.09–49.41 | |
| Median (IQR) | | | | | | | | | |
| 16-24 | 777 | 133 (69–182) | | 827 | 121 (67–188) | | 888 | 118 (67–182) | |
| 25–49 | 491 | 43.8 | | 42.6–46.6 | | 4313 | 4.40 | | 4.36–4.43 | |
| 50+ | 491 | 43.8 | | 42.6–46.6 | | 4313 | 4.40 | | 4.36–4.43 | |

CI, confidence interval; IQR, interquartile range.

*egFR, estimated glomerular filtration rate: calculated using 4-variable MDRD equation (without ethnicity correction).

doi:10.1371/journal.pone.0021795.t001

PLoS ONE | www.plosone.org 3 July 2011 | Volume 6 | Issue 7 | e21795
50 years and above (19.6% vs 11.1% and 16.9% in 16–24 year olds and 25–49 years olds respectively). Almost half of all those who initiated with CD4 cell count <50 cells/µl (45.2%) failed to attain a CD4 cell count >200 cells/µl at 12 months. Proportions with CD4 cell counts below 200 cells/µl at specified time points post ART initiation are displayed in Figure 2B.

Virological suppression

From the 5625 patients recorded as active at 12 months post-ART initiation, 3809 (67.8%) viral loads were available for analysis. Overall 86.3% had a good virological response (<400 copies/ml). A greater proportion of older adults (90.1%, 95% CI 84.7–87.0) had a good response compared to younger adults (81.7%, 95% CI 77.4–86.1 and 86.2%, 95% CI 85.0–87.5 in 16–24 year olds and 25–49 year olds respectively).

Factors associated with mortality

0–3 months. Using age stratified and time split analysis, from the total 997 deaths, 449 occurred in the first three months after ART initiation (very early mortality) giving the highest period mortality rates of 20.9 and 27.1 per 100 person years in younger and older adults respectively (P = 0.037). However, although mortality risk was significantly higher in the older age group, within each age group, age did not have an independent association with mortality. There was strong evidence of an association between male sex, markers of advanced disease at initiation (CD4 cell count <50 cells/µl, higher log10 viral load, lower weight, and albumin <32 g/L) and increased very early mortality in both age groups. In younger adults, but not in older adults, there were additional associations with WHO stage 3/4, low haemoglobin, and renal impairment (Table 3).

3–12 months. Three hundred and twenty deaths; 269 (12.8%) in younger and 51 (20%) in older adults occurred between 3–12 months (early mortality), mortality rates remaining higher in older compared to younger adults (9.5 vs 5.8 per 100 person years respectively; p = 0.001). Low baseline CD4 cell count <50 cells/µl, higher log10 viral load, lower weight, and albumin <32 g/L and increased very early mortality in both age groups. In younger adults, but not in older adults, there were additional associations with WHO stage 3/4, low haemoglobin, and renal impairment (Table 3).

After 12 months. Factors associated with mortality after 12 months were explored in a single model incorporating all ages because of the similar mortality rates in both age strata. As such in the adjusted model (Table 4) mortality risk was not significantly different for older adults compared to younger adults (adjusted hazard ratio [aHR] 1.01, 95% CI 0.66–1.55). There was no longer any evidence of an association with baseline CD4 cell count, but a lower absolute CD4 cell count and a reduced increment at 12 months post ART initiation were both associated with higher mortality.

In all models there was no statistically significant association between mortality and either education or employment.
Figure 2. Age and immune response to ART. A. Median CD4 cell count (cells/μl) over time since ART initiation, stratified by age at ART initiation.

B. Proportion of patients failing to achieve a CD4 count >200 cells/μl at pre-defined time points post ART initiation, stratified by age at initiation.
doi:10.1371/journal.pone.0021795.g002

Table 3. Independent risk factors for very early (0–3 months after ART initiation) and early (3–12 months) mortality stratified by age.

| Variable                  | Very early mortality (0–3 months) | Early mortality (3–12 months) |
|---------------------------|----------------------------------|-------------------------------|
|                          | <50 years (n = 7927) | ≥50 years (n = 919) | <50 years (n = 7154) | ≥50 years (n = 832) |
| Age (1yr increase)        |                                |                               |                           |                           |
| 25–49 years               | 1                               | 1                             | 1.03 (0.99–1.08)         |
| 16–24 years               | 0.79 (0.54–1.34)                 | 0.73 (0.45–1.19)             |
| Male sex                  | 1.64 (1.32–2.03)                 | 1.84 (1.06–3.17)             | 1.40 (1.09–1.80)         | 1.33 (0.73–2.41)         |
| WHO stage 3 or 4          | 1.77 (1.11–2.81)                 | NS                            | 2.06 (1.19–3.57)         | NS                        |
| CD4 cell count (cells/μl) |                                |                               |                           |                           |
| 150–200                   | 1                               | 1                             | 1                          |
| 100–149                   | 1.22 (0.79–1.88)                 | 1.03 (0.37–2.86)             | 1.04 (0.65–1.68)         | 1.73 (0.70–4.26)         |
| 50–99                     | 1.57 (1.05–2.33)                 | 2.34 (0.97–5.87)             | 1.50 (0.97–2.31)         | 1.97 (0.79–4.87)         |
| ≤50                       | 2.38 (1.63–3.46)                 | 2.60 (1.07–6.31)             | 2.76 (1.85–4.10)         | 2.00 (0.80–4.98)         |
| >200                      | 1.56 (0.96–2.52)                 | 1.19 (0.35–4.05)             | 1.50 (0.90–2.51)         | 2.19 (0.83–5.82)         |
| Missing                   | 2.12 (1.16–3.87)                 | 3.97 (1.10–14.4)            | 1.80 (0.92–3.51)         | 0.30 (0.04–2.63)         |
| Viral load (per log₁₀ increase) | 1.16 (1.03–1.34) | 2.28 (1.52–3.43) | NS                        | NS                        |
| Weight (1kg increase)     | 0.94 (0.93–0.95)                 | 0.96 (0.94–0.99)             | 0.99 (0.97–1.00)         | NS                        |
| TB treatment*             | 1.59 (0.84–1.97)                 | 0.90 (0.48–1.69)             | 1.05 (0.79–1.40)         | 1.38 (0.72–2.63)         |
| Haemoglobin <8g/dL        | 2.06 (1.61–2.64)                 | NS                            | NS                        | 4.15 (1.79–9.65)         |
| eGFR ≤60 ml/min/1.73m²†   | 1.73 (1.35–2.23)                 | NS                            | 1.41 (1.00–1.98)         | NS                        |
| Albumin <32g/L            | 3.58 (2.44–5.24)                 | 2.56 (1.19–5.58)             | 2.17 (1.56–3.02)         | 1.52 (0.76–3.02)         |
| missing                   | 4.38 (1.88–10.19)                | 0.67 (0.42–10.58)            | NS                        | NS                        |

Cox regression models split by time under observation (person years) into very early mortality (0–3 months) and early mortality (3–12 months). Risk factors determined separately for age groups <50 years and ≥50 years.

All values are adjusted hazard ratios with 95% confidence interval.

NS, not significant in univariable model.

*Concurrent TB treatment at time of ART initiation.

†eGFR, estimated glomerular filtration rate: calculated using 4-variable MDRD equation (without ethnicity correction).
doi:10.1371/journal.pone.0021795.t003
Table 4. Independent predictors of mortality after the first 12 months of ART (N = 5625).

| Variable | aHR | 95% CI |
|----------|-----|--------|
| Age 25–49 years | 1 | 1 |
| ≥50 years | 1.01 | 0.66–1.55 |
| 16–24 years | 1.35 | 0.86–2.14 |
| Male sex | 1.95 | 1.46–2.57 |
| Baseline WHO stage 3/4 | 2.72 | 1.49–4.97 |
| Missing | 2.62 | 1.43–4.83 |
| Baseline CD4 cell count (cells/μl) | | |
| 150–200 | 1 | |
| 100–149 | 0.80 | 0.51–1.25 |
| 50–99 | 1.11 | 0.72–1.71 |
| ≥50 | 1.11 | 0.70–1.75 |
| >200 | 0.65 | 0.38–1.13 |
| Missing | 0.46 | 0.20–1.06 |
| CD4 increment at 6 months (cells/μl) | | |
| <50 | 0.98 | 0.63–1.51 |
| 50–99 | 0.49 | 0.29–0.81 |
| Missing | 1.33 | 0.39–4.59 |
| Absolute CD4 count at 6 months (cells/μl) | | |
| >350 | 1 | |
| 201–350 | 1.45 | 0.81–2.57 |
| ≥200 | 0.91 | 0.44–1.90 |
| CD4 increment at 12 months (cells/μl) | | |
| <50 | 0.41 | 0.23–0.73 |
| 50–99 | 0.46 | 0.24–0.88 |
| ≥100 | | |
| Missing | 6.15 | 1.69–22.38 |
| Absolute CD4 count at 12 months (cells/μl) | | |
| >350 | 1 | |
| 201–350 | 0.81 | 0.43–1.54 |
| ≥200 | 1.49 | 0.73–3.03 |
| Viral load at 12 months (copies/ml) | | |
| <400 | 2.67 | 1.78–4.02 |
| ≥400 | | |
| Missing | 1.74 | 1.26–2.41 |

aHR, adjusted hazard ratio; CI, confidence interval.
Risk factors determined through Cox proportional hazards regression techniques, assessing mortality after 12 months post ART initiation, conditional on being active on the treatment programme at 12 months.

Sensitivity analysis
Mortality rates did not differ significantly between those with complete baseline observations compared to those with missing observations. However, 116 (6.4%) of 1816 patients alive but with a missing viral load at 12 months subsequently died compared to 112 (2.9%) of 3809 with a recorded viral load (P<0.001), whilst 103 (7.1%) of those alive but with a missing CD4 cell count at 12 months post ART initiation died compared to 125 (3.0%) of those with a recorded CD4 count (P<0.001), resulting in higher mortality risk in some of these missing categories (Table 4).

Overall loss to follow-up was 12.9%; 11.6% and 6.5% in the 16–24 yrs, 25–49 yrs, and ≥50 yrs age groups respectively (p<0.01). Despite these differences, the sensitivity Kaplan Meier and Cox regression analysis results did not differ significantly from those obtained using completely observed data.

Discussion
We used a large rural HIV treatment programme in South Africa, with a comprehensive tracking system for patients lost to follow-up, to assess mortality rates and differences in three population groups defined by age. In this analysis of 8846 adults with 997 deaths, overall mortality risk was 32% higher for those who initiated ART at age ≥50 years compared to those initiating at age 25–49. Although consistent with previous reports from urban African settings [13,14] we show that this mortality difference is only evident in the first year of ART, following which mortality rates in older adults are no longer different from that in younger adults despite only modest CD4 count reconstitution in the older age group. Previous studies from Europe and North America [32,33,34,35] have also reported poorer immunological but better virological responses in older compared to younger adults but have not explored how these may relate to mortality rates in older age groups receiving ART. Our study shows that despite older adults having a lower proportion of individuals achieving good immunological response in the first year on ART, their mortality rate as a group, after 12 months on ART, was similar to that observed in the younger adult group. This finding coupled with the fact that older adults had a higher proportion of individuals achieving optimal viral suppression, might imply that in older adults, the degree of CD4 count reconstitution may matter less once HIV has been suppressed. Mortality was not significantly associated to either education or employment probably because in this population there is not much heterogeneity in socio-economic variables and everyone is poor [22].

The majority of people enrolled in HIV care and treatment programmes in sub-Saharan Africa are younger adults, consistent with prevalence patterns [37]. In this programme, just over 10% of adults who initiated ART during the study period were ≥50 years old. The higher proportion of males is contrary to the treatment programme in general but is consistent with local prevalence data that shows more males being infected later in life hence expected to access care much later than females [4,23]. Whilst evidence from high-resource settings has suggested that older adults present with more advanced disease [33,38,39], our data suggest the opposite with a higher median CD4 cell count and lower proportion with CD4 cell count <50 cells/μl in older adults. The most striking clinical difference between the groups at baseline was the higher proportion of renal dysfunction at baseline, with 37% of older adults having an estimated glomerular filtration rate (eGFR) of ≤60 ml/min/1.73 m². Consistent with the observed decline in GFR with age, this alerts us to the high frequency of renal disease in this setting which is not always detected with serum creatinine measurements alone [40].

In all age groups, the highest mortality rates were in the first three months of ART in line with data previously published from this and other programmes [23,41,42,43,44]. Very early and early mortality was higher in older adults, although older adults presented for ART initiation with higher CD4 counts than younger adults. High early mortality mainly associated with...
advanced disease coupled with blunted immunologic response in older adults raises an important question of whether older adults should initiate ART at higher CD4 count threshold compared to younger adults and calls for interventions to encourage early presentation for ART. Older adults may also potentially benefit from enhanced clinical care during initial phases of ART.

The high number of deaths immediately after ART initiation suggests that this mortality is still driven largely by HIV disease itself. However, for older adults, the higher mortality may be explained by higher prevalence of non-HIV conditions such as cardiovascular diseases and diabetes. Unfortunately we were unable to ascertain the cause of death since this information within the programme was extremely limited, with only 42 of 997 deaths (4.2%) attributed to a specific cause. However, research in similar settings has shown mortality in the first year of ART to be caused predominantly by infectious diseases related to immunosuppression with tuberculosis consistently shown to be the leading cause of death across all age groups followed by cryptococcal disease and other infectious diseases [18,19,44,45]. Although in previous analyses we showed that younger age was associated with higher TB incidence in the first three months of ART [36], it could be that TB presentation is different in older adults or that symptoms are less frequently attributed to TB in this group leading to missed diagnoses and mortality [46]. The contribution of immune reconstitution inflammatory syndrome (IRIS) to early mortality remains unclear; a recent meta-analysis, using data from diverse settings across high-, middle- and low-income settings, suggested that IRIS might be responsible for 21% of all deaths after ART initiation [47]. Whether the incidence, presentation or mortality attributable to IRIS is higher in older adults requires further study.

Our study demonstrates that at 12 months, approximately one-quarter of our cohort had CD4 cell count \( \leq 200 \) cells/\( \mu l \) with the largest proportion and the poorest immunological response in those aged \( \geq 50 \) years and this was associated with increased risk of subsequent death. Larger CD4 count increases were significantly associated with reduced mortality risk irrespective of recent absolute CD4 count. In addition, previous absolute CD4 cell thresholds (CD4 cell count at 6 months after ART initiation) were not associated with mortality although CD4 count increments of greater than 100 cells/\( \mu l \) at this stage decreased mortality risk beyond a year on therapy. This may possibly imply that as long as there is an immune response greater than a certain threshold, the inflation of the absolute CD4 cells count on mortality becomes minimal and non-significant. Despite younger adults demonstrating superior immunological responses, they had inferior virological suppression, a finding that supports previous observations [32,33,34,35], and was associated with a nearly threefold increased risk of mortality after the first year on therapy. Hence the increased risk in older adults associated with poorer immunologic response may have been counteracted by the reduced risk associated with superior virological response resulting in equal mortality risk in both age groups after one year of ART. Although it is possible that this lack of mortality difference may be due to limited statistical power, there are also possible reasons why this may be; the fact that these older adults are seen every 30 days by health care personnel when they come to collect ART may mean that they have a better chance of early diagnosis of age driven morbidities and better clinical management of new and existing morbidities hence limiting the effect of age on mortality. Babiker et al previously suggested that the effect of age on mortality could be attenuated in the HAART era if there was proportionately a reduction in mortality in older age groups. As older adults are at higher risk of HIV mortality primarily due to a faster decline in CD4 cell counts, HAART associated increases in CD4 could have a larger impact in reducing mortality in an older population [6].

Our study population is similar to that from many rural public health HIV treatment programmes and therefore our results are likely generalisable to similar settings in sub-Saharan Africa. The large cohort size and high mortality rates have enabled this analysis [23]. A major strength of our programme is the comprehensive tracking system for patients lost to follow-up which ensures that deaths are ascertained contemporaneously, unlike in many other programmes [48], giving us confidence that our mortality rates are representative of the true population mortality rates.

Our study has certain limitations as a retrospective analysis of routine programmatic data; we were hampered by missing results particularly for follow-up CD4 cell counts and viral loads which we attempted to address by interpolation of missing CD4 cell counts. The blunted immunological response in older adults compared to younger adults might have been underestimated because CD4 cell count changes are influenced by survival bias, i.e. individuals with the worst immunological response are more likely to have died. Although we controlled for multiple biological variables in determining factors associated with mortality, there might still be residual confounding by adherence levels or other unmeasured variables.

Extremely high mortality rates in the first year of ART, more so for older adults suggests that strategies to reduce this early mortality need to be implemented and evaluated with a degree of urgency and that the needs of older adults should be considered within these strategies. Medical interventions, particularly intensive screening and treatment for TB and cryptococcal infection should be implemented and evaluated to improve understanding of the epidemiology of these infections in older adults [49]. Better understanding of the current patterns of testing and health care usage amongst older adults will inform on appropriate age-specific interventions. Making HIV services more acceptable for this age group might get them into HIV care at an earlier stage. We have previously shown lower rates of retention in pre-ART care for older adults [50]; with the known association between older age and more rapid CD4 decline, it is necessary to explore alternative care strategies, which might include integration with other chronic disease management or community-based follow-up [51]. Further work is ongoing within our programme to determine the causes of death and the burden of co-morbidities in the older population. Future work is required to evaluate whether more intensive follow-up impacts on mortality for individuals at high-risk of death in the first few months of ART.

Discussion around older adults and the HIV epidemic in sub-Saharan Africa often only focus on the indirect impact of the epidemic. Our finding of higher mortality on ART for older adults compared to younger adults adds to the evidence base pointing to a substantial direct effect of HIV on older adults’ health. As we move into the next phase of ART scale-up the challenges of HIV in older people will need to be addressed with more purpose.

Acknowledgments

We thank Kevi Naich and Hilary Thulare (HIV Treatment and Care Programme leaders); Colin Newell (senior database scientist); the Monitoring, Evaluation & Reporting team; and Till Barnighausen (for statistical advice).

Author Contributions

Responsible for study design, data analysis, and drafting the manuscript: PCM RJL. Assisted with data interpretation, and revision of the manuscript: AR. Provided critical oversight throughout the process of study design, data analysis, and manuscript preparation: MLN. Wrote the manuscript: PCM RJL. All authors approved the final version of the manuscript.
References
1. Schmid GP, Williams BG, Garcia-Calleja JM, Miller C, Segar E, et al. (2009) The unexplored story of HIV and ageing. Bull World Health Organ 87: 162–162A.
2. UNAIDS (2008) Report on the global HIV/AIDS epidemic 2008. Geneva, Switzerland.
3. UNAIDS (2006) Understanding the latest estimates of the 2006 report on the global AIDS epidemic.
4. Zachariah R, Roka T, Bhausen T, Newell M-L (2010)High rates of AIDS-related mortality among older adults in rural Kenya. J Acquir Immune Defic Syndr 55: 239–242.
5. Babiker AG, Porto T, Porter K, Walker AS, Darbyshire JH (2001) Age as a determinant of survival in HIV infection. J Clin Epidemiol 54(Suppl 1): S16–21.
6. van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ (2008) Estimating HIV infection of concern also in people 50 years and older in rural South Africa. S Afr Med J.
7. Negin J, Wariero J, Cumming RG, Mutuo P, Pronyk PM (2010)High rates of AIDS-related mortality among elderly in rural Kenya. J Acquir Immune Defic Syndr 55: 239–242.
8. Wandel S, Egger M, Rangun R, Nelson K, Costello C, et al. (2008) Duration from seroconversion to death: a retrospective analysis in six South African and middle-income countries: collaborative analysis of prospective studies. Sex Transm Infect 84(Suppl 1): 31–36.
9. Houben RJ, Seoane DB, Nel G, Bester A, Shearer S, et al. (2007) Survival from HIV-1 serocconversion in Southern Africa: a retrospective cohort study in nearly 2000 gold-miners over 10 years of follow-up. AIDS 21: 625–632.
10. Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, et al. (2007) Time from HIV-1 seroconversion to death: a collaborative analysis in southern African and middle-income countries before highly active antiretroviral therapy. AIDS 21(Suppl 6): S55–63.
11. Van der Paal L, Shafer LA, Todd J, Mayanja BN, Whitworth JA, et al. (2007) HIV-1 disease progression and mortality before the introduction of highly active antiretroviral therapy in rural Uganda. AIDS 21(Suppl 6): S21–29.
12. Lown SD, Little F, Bekker LG, Kaplan R, Campbell E, et al. (2009) Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. AIDS 23: 335–342.
13. Touré S, Kosarad S, Seyler C, Traore S, Dakoury-Dogbo N, et al. (2008) Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d’Ivoire: 2-year outcomes and determinants. AIDS 22: 873–882.
14. Tshu SM, Pacheco AG, Harrison LH, Stone MA, May M, et al. (2010) Mortality associated with discordant responses to antiretroviral therapy in resource-constrained settings. J Acquir Immune Defic Syndr 55: 70–77.
15. Fairall LR, Bachmann MO, Louwagie GM, van Vuuren C, Chikobvu P, et al. (2008) Effectiveness of antiretroviral treatment in a South African program: a cohort study. Arch Intern Med 168: 86–93.
16. Brinkhof MW, Boule A, Weigel S, Memis E, Mathers C, et al. (2009) Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-uninfected mortality. PLoS Med 6: e1000066.
17. Brinkhof MW, Dabis F, Myer L, Bangsberg DR, Boule A, et al. (2008) Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ 86: 559–567.
18. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, et al. (2006) Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. Jamaica 296: 782–793.
19. Etard JF, Nkiali A, Thiery-Mieg M, Gueye NF, Gueye PM, et al. (2006) Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. AIDS 20: 1181–1189.
20. MacPherson P, Zuckel A, Martinson N, Pronyk PM (2009) Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg 103: 588–593.
21. Levey AS, Greene T, Kissel JW, Beck GJ (2000) A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 11: 155A.
22. van Deventer HF, George JA, Paiker JE, Becker PJ, Katz J (2000) Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. Clin Chem 54: 1197–1202.
23. Mutevedzi PC, Barnighausen T, Newell M-L (2010)High rates of AIDS-related mortality among adults aged 50 years and over. AIDS 24: 2109–2115.
24. Grobusch PM, Thurneux TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81: 515–526.
25. The Collaboration of Observational HIV Epidemiological Research (COHERE) study group (2009) Response to combination antiretroviral therapy: variation by age. AIDS 22: 1463–1473.
26. Grabar S, Kossiagian I, Sobel A, Le Bras P, Gasnault J, et al. (2004) Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. AIDS 18: 2029–2038.
27. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, et al. (2007) Older age and the response to and tolerability of antiretroviral therapy. Arch Intern Med 167: 684–691.
28. Houlahan CF, Mutevedzi PC, Lesles RJ, Cooke GS, Tanser FC, et al. (2010) The tuberculosis challenge in a rural South African HIV programme. BMC Infect Dis 10: 23.
29. Welz T, Hoenegod V, Jaffar S, Batsig-Freinjenbaum J, Herbst K, et al. (2007) Comparison of very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. AIDS 21: 1467–1472.
30. Grabar S, Weiss L, Costagliola D (2006) HIV infection in older patients in the HAART era. J Antimicrob Chemother 57: 4–7.
31. Sabin CA, Smith CJ, Gumley H, Murphy G, Lampe FC, et al. (2004) Late presenters in the era of highly active antiretroviral therapy: uptake of and responses to antiretroviral therapy. AIDS 18: 2145–2151.
32. Franey C, Keston D, Barnighausen T, Dedicoat M, Adam A, et al. (2009) Renal impairment in a rural African antiretroviral programme. BMC Infect Dis 9: 143.
33. Boulle A, Bock P, Oder M, Cohen K, Channing L, et al. (2008) Antiretroviral therapy and early mortality in South Africa. Bull World Health Organ 86: 670–678.
34. Bell A, Poot J, Myer L, Bekker LG, et al. (2006) Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 367: 817–821.
35. Lawn SD, Myer L, Haeling G, Orrell C, Bekker LG, et al. (2006) Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. Clin Infect Dis 43: 770–776.
36. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R (2003) Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. AIDS 19: 2141–2148.
37. Castelnuovo B, Manabe YC, Kiragga A, Kamya M, Easterbrook P, et al. (2009) Cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome in the first 5 years of antiretroviral therapy initiation in an urban African cohort. Clin Infect Dis 49: 965–972.
38. Negin J, Cumming RG (2010) HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. Bull World Health Organ 88: 947–953.
39. Muller M, Wandel S, Colebunders R, Atta S, Furrer H, et al. (2010) Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 10: 251–261.
40. Brinkhof MW, Pujades-Rodriguez M, Egger M (2009) Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One 4: e5790.
41. Lawn SD, Harries AD, Wood R (2010) Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings. Curr Opin HIV AIDS 5: 18–26.
42. Sabin CA, Mutevedzi PC, Cooke GS, Newell M-L (2010)Prescription retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr.