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Poorer ART Outcomes with Increasing Age at a Large Public Sector HIV Clinic in Johannesburg, South Africa

Mhairi MASKEW[1,¶], **Alana T. BRENNAN**[2,3], **A. Patrick MACPHAIL**[1,4], **Ian M. SANNE**[1,4], and **Matthew P. FOX**[2,3,5]

[1]Clinical HIV Research Unit, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa

[2]Center for Global Health and Development, Boston University, Boston, MA, USA

[3]Health Economics and Epidemiology Research Office, University of the Witwatersrand, Johannesburg, South Africa

[4]Right to Care, Johannesburg, South Africa

[5]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Background—As the current HIV-positive population ages, the absolute number of patients >50 years on treatment is increasing.

Methods—We analyse differences in treatment outcomes by age category (18-29, 30-39, 40-49, 50-59 and ≥60) among 9139 HIV-positive adults initiating ART in South Africa.

Results—The adjusted hazard ratios for all-cause mortality increased with increasing age, with the strongest association in the first 12-months of follow-up amongst 50-59 (HR 1.67; 95% CI: 1.24-2.23) vs. those <30. However, patients 50-59 years were less likely to be lost during 24-months on ART (HR 0.75; 95% CI: 0.59-0.94) vs. <30. By 6- and 12-months on treatment, older patients were less likely to increase their CD4 count by ≥50 cells/mm^3.

Conclusion—While older patients are at higher risk of mortality and have poorer immunological responses than their younger counterparts, they are more likely to adhere to care and treatment in the first 24-months on ART.

[¶]**Corresponding Author Details:** Johannesburg Address: Clinical HIV Research Unit, Suite 176, Private Bag x2600, Houghton, 2041, South Africa, Phone: +27-11-276-8800, Fax: +27-11-482-2130, mmaskew@witshealth.co.za.
Co-author contact details:
AT Brennan: abrennan@heroza.org, Phone: +27112768928
AP MacPhail: patrick.macphail@righttocare.org, Phone +27137500781
IM Sanne: isanne@witshealth.co.za, Phone: +27112768800
MP Fox: mfox@bu.edu, Phone: +27112768800

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Author Contributions:
MM and MF designed the study and along with AB analyzed and interpreted the data and drafted the first manuscript. PM and IS contributed to acquisition of the data and administrative support. All authors provided critical revision of the manuscript for important intellectual content and have read and approved the text as submitted.

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Keywords

HIV; age; antiretroviral; mortality; treatment response; loss to follow-up

BACKGROUND

The average age of patients starting antiretroviral therapy (ART) in resource-limited settings is below 40 years [1, 2]; however, as the current HIV-positive population ages and as access to treatment increases in resource-limited settings, the absolute number of older patients on treatment is increasing. Few studies have explored outcomes of older patients on ART specifically in resource-limited settings. Research in developed countries has shown that older HIV-positive individuals' progress faster from AIDS diagnosis to death or morbidity compared to younger populations [3]. However, there is mixed evidence as to whether older HIV-infected patients have a higher risk of mortality or different immunological or virologic responses to ART [4-20]. In resource-limited settings like South Africa, few clinics have enough data for patients over 50 years to have adequate power to determine if outcomes differ among higher age groups.

The Themba Lethu Clinic in Johannesburg, South Africa is one of the largest HIV clinics in the country, with 968 patients ≥50 years initiated onto ART between April 2004 to December 2008. We explored whether treatment outcomes, including failure to achieve immunological response and virologic suppression on ART, differ with increasing age amongst HIV-positive patients.

METHODS

Cohort Description

The study was conducted at Themba Lethu Clinic in Johannesburg, South Africa which enrolled over 18,800 patients in care between 2004 and 2008; over 12,000 of those have initiated ART. Care at Themba Lethu Clinic is provided according to South African National Department of Health guidelines [21]. All patient data at Themba Lethu Clinic is collected and stored in a standardized way using an electronic patient management system (TherapyEdge-HIV™). Demographic, clinical history and examination data as well as laboratory results (including CD4 counts, full blood counts and liver function tests) are captured at initiation of first-line ART. At each subsequent medical visit, information on regimen changes, tuberculosis symptom screen, weight, other vital signs and any new clinical conditions diagnosed including new opportunistic infections is recorded. Treatment monitoring is done with CD4 counts and viral loads between four and seven months after initiation of a new regimen (median 3.9 months; IQR 3.7-4.7) and then approximately six monthly thereafter unless clinically indicated. CD4+ T-cell lymphocytes counts are done using pan-leucogated CD4+ flow cytometry (FlowCount Fluorospheres, Beckman Coulter-Immunotech, France) while HIV-1 RNA viral load tests are conducted using NucliSENS EasyQ® HIV-1 assay (bioMérieux Clinical Diagnostics, France). At each medical visit, patients are seen by a nurse, a doctor, and when appropriate, a counselor. All visit information is collected in real-time in the clinic by the clinical staff attending to the patients.

Early on in treatment patients are scheduled for medical visits every month and six-monthly there after once stable; in between these visits, patients return every one to two months to collect ARVs. Visit scheduling is tracked electronically and allows for tracing of patients who have missed visits and for categorization of patients as loss to follow-up (defined as is having missed a scheduled medical or antiretroviral (ARV) pickup for >3 months). Active

tracing of those who miss scheduled clinic visits is attempted by telephonic contact and home based tracing within a month of the missed visit.

Use of Themba Lethu Clinic data was approved by the Human Research Ethics Committee of the University of the Witwatersrand. Approval for analysis of de-identified data was granted by the Boston University Institutional Review Board.

Eligibility Criteria

Our analysis included non-pregnant HIV-infected treatment-naïve patients, ≥18 years of age, who initiated ART at Themba Lethu Clinic between April 2004 to December 2008. We limited the analysis to patients initiated onto standard government first-line ART regimens (stavudine (d4T) or zidovudine (AZT) with lamivudine (3TC) and either efavirenz (EFV) or nevirapine (NVP)) [21].

Study variables

This cohort study compared ART outcomes (all-cause mortality - hereafter referred to as mortality - and loss to follow-up at 12 and 24 months) by age at ART initiation (categorized as 18-29.9, 30-39.9, 40-49.9, 50-59.9 and ≥60 years). We limited outcomes to the first 24-months on treatment as long term mortality would be expected to be higher amongst older patients. We explored the relation between age and failure to achieve a CD4 response and HIV viral load suppression by 6- and 12-months on ART. Mortality is ascertained through the South African National Vital Registration System [22-24].

Statistical analysis

Log-binomial regression was used to estimate the relative risk of age on failure to achieve CD4 response (≥50 cells/mm^3) and failure to suppress viral load (<400 vs. ≥400 copies/ml) by 6- and 12-months on treatment. Cox proportional hazard models were used to estimate hazard of death and loss to follow-up by age category and to identify predictors of mortality and becoming loss to follow-up. For death and loss to follow-up analyses (the only two time to event analyses), person-time accrued from ART initiation until the earliest of: 1) date of death; 2) date of loss to follow-up; 3) date of transfer; or 4) completion of 24 months of follow-up. The proportionality assumption was tested with log (-log(survival probability)) versus time plots for each covariates in the final models and was not violated. Potential confounding factors such as gender, baseline haemoglobin, baseline CD4 count, body mass index (BMI) and World Health Organisation (WHO) clinical stage [25] were included in models where appropriate.

RESULTS

Of the 12,146 patients initiating ART at Themba Lethu Clinic between April 2004 and December 2008, there were 968 aged ≥50 years. We excluded 47 patients <18 years of age, 1857 non-naïve patients, 974 patients on non-standard first-line regimens and 129 pregnant women from the original 12,150 individuals, leaving a sample of 9139 patients eligible for analysis. This included 831 individuals aged ≥50 years who were eligible for further analysis. Patients had a median age of 36.3 years (IQR 31.3-42.5), a baseline CD4 count of 74 cells/mm3 (IQR 27-144), were predominately female (61.8%) and primarily initiated on d4T-3TC-EFV (89.4%). Patients were followed for a median of 24.0 months (IQR 13.5-24.0). We identified 721 (7.9%) patients 50-59.9 years and 110 (1.2%) patients ≥60 years old (Table 1). Although the cohort is predominately female, the proportion of males increases steadily with age, with those ≥60 comprising more males (57.3%) than females. Additionally, older patients, particularly those in the ≥60 category, presented with higher median baseline CD4 counts and BMI and had fewer WHO stage III/IV conditions

compared to younger patients. Greater proportions of patients were initiated on EFV-based regimens with each increasing age category.

Death and Loss to follow-up

Among 9,139 patients, 992 (10.9%) died and 1353 (14.8%) were loss to follow-up during the 24 month follow-up period (Table 1). Median follow-up time for patients that died or were lost was 4.5 months (IQR 1.6-10.1) and 7.2 months (IQR 4.1-14.3), respectively. The proportion of patients who died increased with age. Over 14% of patients ≥60 years old died during follow-up, compared to 9.0% of patients <30 years. The mortality rate increased from 8.6/100 person years in the 18-29 group to 13.5/100 person years among those >60years. We observed a U-shaped relationship between age and proportion loss to follow-up, with patients <30 and ≥60 years having the highest proportion lost (19.0% and 21.0% respectively); while only 14.6% of patients aged 50-59.9 were loss to follow-up.

Adjusted mortality rates at 12- and 24-months increased with increasing age (Table 2). The largest estimate of this association was in the first 12 months of follow-up amongst patients aged 50-59.9 years (HR 1.67; 95% CI: 1.24-2.23) and, although imprecise, patients ≥60 years (HR 1.54; 95% CI: 0.81-2.95) vs. <30 year olds had a higher risk of death. Relative increases in risk of death were similar when follow-up was extended to 24 months. Other predictors of mortality within the first 12 months included male gender (HR 1.23; 95% CI: 1.06-1.42), initiating CD4 count <50cells/mm^3 (HR 2.11; 95% CI: 1.60-2.79), anaemia (Hb <10.0 ug/dL) at ART initiation (HR 1.71; 95% CI: 1.47-1.99) and baseline WHO stage III/IV condition (HR 1.21; 95% CI: 1.04-1.42). Predictors of mortality were similar at 24 months.

In adjusted models, older patients were less likely to become loss to follow-up over 12 months on ART, specifically among patients 30-39.9, 40-49.9 and 50-59.9 years (HR 0.84; 95% CI: 0.71-1.00, HR 0.84; 95% CI: 0.61-1.07 and HR 0.81; 95% CI: 0.61-1.07, respectively) vs. <30, though these estimates were somewhat imprecise (Table 2). These hazard ratios moved farther from the null by 24 months of follow-up for all three age groups. Additionally, we found that male gender (HR 1.32; 95% CI: 1.15-1.52), anaemia at ART initiation (HR 1.76; 95% CI: 1.53-2.04) and low baseline BMI (HR 1.56; 95% CI: 1.35-1.80) were important predictors of becoming loss to follow-up by 12 months after ART initiation. These results were similar at 24 months of follow-up.

Immunological and Virologic Response

Of the 7652 who were alive and in care at 6 months, 1358 (17.7%) individuals were missing CD4 counts and 1760 (23%) were missing VL results. Older age categories were equally likely to have missing values compared the youngest group. By six months on treatment, the adjusted relative risk (aRR) for failure to achieve a CD4 increase of ≥50cells/mm^3 was greater for older patients (50-59.9 and ≥60) (aRR 1.43; 95% CI: 1.18-1.72 and aRR 1.44; 95% CI: 1.01-2.06, respectively) vs. patients <30 years of age (Table 3). Older age categories also gained, on average, fewer CD4 cells by 6 months on treatment compared to younger age groups. Those aged <30 years gained 40 cells (95% CI: 14-66), 36 cells (95% CI: 7-65), 53 cells (95% CI: 13-94) and 67 cells (95% CI: -23-156) more than the 30-39, 40-49, 50-59 and >60 groups respectively.

Adjusted relative risk for failure to achieve viral load suppression by six months on treatment for patients 40-49.9 and 50-59.9 vs. those <30 years old were 0.75 (95% CI: 0.58-0.98) and 0.80 (95% CI: 0.55-1.17), respectively. The point estimates, though less precise due to smaller numbers at this time point, were further from the null after 12 months among patients ≥60 years (aRR 0.67; 95% CI: 0.22-2.05).

DISCUSSION

As few HIV cohorts in resource-limited settings have a large enough population >50 years of age on ART, this study is one of the first to investigate differences in treatment outcomes among HIV-positive adults initiating ART >50 years of age compared to younger patients in such settings. As expected, older subjects had a higher risk of mortality at 12 and 24 months. Although we estimate all-cause mortality, HIV and treatment-related factors have been shown to exceed what is considered normal aging in the development of hypertension, hypertriglyceridemia, low bone mineral density, and lipodystrophy [26]. In addition, we found that older age groups mounted a poorer immunological response to treatment by 6 and 12 months of follow-up. However, older subjects had a lower risk of becoming loss to follow-up (except in the highest age band where the estimate was imprecise) and some older age groups fared better in terms of viral load suppression.

While age-related decline in immune function occurs as part of the natural physiological ageing process, there have been concerns regarding the impact that this declining immunity will have on the already immune-compromised HIV-infected older patient [27]. There is evidence that older patients mount poorer CD4 cell count responses than their younger counterparts [4-7, 28, 29] and our results from this resource limited setting agree with these findings. Those aged ≥60 were most at risk – this group was nearly three times as likely to fail to achieve a CD4 count response compared to those 18-29.9. This was despite the fact that the ≥60 group presented for care with fewer signs of advanced disease (CD4 count and WHO stage III/IV clinical conditions) than any other age category including those aged 50-59.9. While our analysis of viral suppression lacked precision, our findings concur with previous work on viral load suppression and age [8, 11-12, 14-15, 18, 28-29] suggesting an advantage for older age groups. This advantage may potentially be mediated through improved adherence to ART among older populations [13, 28].

In our cohort, the proportion of males increased steadily with age. This is in keeping with demographic trends of the age distribution of HIV prevalence in South Africa [30] which likely reflect the intergenerational and age-disparate trends in sexual relations sex patterns (older men have sex with younger women) [31-33] in this population. Older individuals were also more likely to be employed than the younger patients potentially representing a more stable population than their younger counterparts. This may also explain the lower rates of loss to follow-up evident among older age groups. Patients who regularly attend their scheduled medical and pharmacy visits are likely to be adherent to treatment and as a result have better ART outcomes [34, 35]. Achieving a high level of ART adherence among older patients is notable considering this population typically have multiple co-morbidities due to other age-related chronic illness and subsequently already have high pill burdens.

EFV-based regimens appeared to be favoured over NVP-based regimens with each increasing age category. NVP is preferred in women who are pregnant or planning to become pregnant. Efavirenz is considered potentially teratogenic and concerns have been raised regarding the potential for neural tube defects in the unborn child if used in the first trimester [36]. Older women are less likely to be pregnant and there were also fewer women in the older age categories as well. This is the likely reason for the increasing use of EFV with age. There is mixed evidence that the outcomes of those receiving EFV are different to those receiving NVP. Some show superior outcomes for those receiving EFV [37-39] while a Cochrane review concluded there was no difference in terms of virologic suppression and a 2 cell difference in mean change in CD4 count over 48 weeks of follow up [40]. If differences in outcomes exist between these treatment groups, it may have confounded the estimates of the effect of age on the clinical outcomes measured. Our results did not,

however, suggest any advantage for EFV based regimens. Additionally all models were adjusted for ART regimen, so any confounding due to ART regimen is likely to be minimal.

Our findings should be considered in light of the study limitations. First, although the study site is one of the largest in South Africa, this study represents patients from only one government ART site, and therefore may not be generalized to all patients attending national HIV clinics or those in the private sector. Similarly the generalizability of this data to settings in the developed world may be limited given the differences in ART regimens used in the developing world. Second, the small sample size in our oldest age group (≥60 years) may have limited our ability to accurately estimate outcomes in this group and so we interpret these results with caution. Third, we estimate all-cause mortality and are unable to report on HIV-related cause of death versus other causes for this population. Also, the ascertainment of mortality at 24 months may be underestimated as linkage to the South African National Vital Registration System was performed prior to 2010. However, the proportion of valid national ID numbers and the likelihood of having a death ascertained in this manner were similar for all age categories and are unlikely to have biased these results strongly. Finally, we had to rely on surrogate markers of adherence which may have limited our assessment of its role.

CONCLUSION

The focus of HIV treatment is shifting from an acute to a more chronic approach to disease management for the increasing life expectancy of those affected. This, combined with an increasing number of older HIV-positive persons on ART, has implications for the treatment of these patients. Our findings and those of others, suggest there may be benefits to having age-specific ART guidelines [41]. In light of the increased risk of mortality and poorer immune response to ART demonstrated by older patients, creating eligibility criteria allowing older patients to initiate ART at higher CD4 cell counts could improve outcomes in these high-risk age groups. Financial constraints are always to be considered in implementation of such a recommendation particularly in resource limited settings. Though this subset of the population accessing ART is currently small in terms of absolute numbers in resource-limited settings, these individuals often play a vital caregiver and economic role in their families [42-43]. Improvement in treatment outcomes after initiation of ART among older persons could therefore impact beyond the clinical improvement of an individual to the wellbeing of an entire family. Additional research would be required to determine the immunological criteria for initiation of ART in older HIV infected adults necessary to realize this potential in outcomes improvement.

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Table 1

Baseline characteristics and outcomes by 24-months on ART Stratified by Age for patients at the Themba Lethu Clinic in Johannesburg, South Africa (n=9139)

		Age Group (years)				
Characteristics		**18-29.9**	**30-39.9**	**40-49.9**	**50-59.9**	**≥60**
Sex, n (%)	Female	1340 (77.1)	2586 (60.1)	1289 (56.8)	385 (53.4)	47 (42.7)
	Male	398 (22.9)	1716 (39.9)	979 (43.2)	336 (46.6)	63 (57.3)
Employed, n (%)	Yes	562 (32.3)	1922 (44.7)	1107 (48.8)	310 (43.0)	41 (37.3)
	No	1176 (67.7)	2380 (55.3)	1161 (51.2)	411 (57)	69 (62.7)
CD4 cell count at ART	0-50	630 (36.3)	1577 (36.7)	754 (33.2)	205 (29.4)	27 (26.0)
Initiation (cells/mm^3), n (%)	51-100	301 (17.3)	822 (19.1)	422 (18.6)	185 (25.7)	27 (26.0)
	101-200	545 (31.4)	1230 (28.6)	712 (31.4)	225 (31.2)	42 (30.4)
	200-350	109 (6.3)	253 (5.9)	145 (6.4)	43 (6.0)	8 (7.7)
	Missing	153 (8.8)	420 (9.8)	235 (10.4)	63 (8.7)	6 (5.5)
WHO Stage at ART Initiation, n (%)	I/II	883 (50.8)	2225 (51.7)	1224 (54.0)	399 (55.3)	73 (66.4)
	III	706 (40.6)	1706 (39.7)	863 (38.0)	258 (35.8)	29 (26.4)
	IV	149 (8.6)	371 (8.6)	181 (8.0)	64 (8.9)	8 (7.3)
First-line ART Regimen, n (%)	d4T/3TC/EFV	1463 (84.2)	3831 (89.0)	2093 (92.3)	675 (93.6)	107 (97.3)
	d4T/3TC/NVP	238 (13.7)	320 (7.4)	93 (4.1)	18 (2.5)	0 (0.0)
	Other	37 (2.1)	151 (3.5)	82 (3.6)	28 (3.9)	3 (2.7)
CD4 at ART Initiation (cells/mm^3)	Median (IQR)	74 (23-145.0)	70 (24-141)	79 (30-148)	84.5 (39-144)	97.5 (47-157.5)
Follow-up Time (months)	Median (IQR)	24.0 (12.9-24.0) 24.0 (14.4-24.0)		24.0 (13.8-24.0) 24.0 (11.8-24.0)		24.0 (8.8-24.0)
Hb at ART Initiation (ug/dl)	Median (IQR)	11.2 (9.6-12.7)	11.5 (9.8-12.9)	11.6 (10.1-13.1) 11.7 (10.2-13.2)		11.4 (10.3-13.1)
BMI at ART Initiation	Median (IQR)	20.5 (18.2-23.2) 21.3 (18.9-24.3)		21.6 (19.3-24.8) 21.5 (18.8-24.7)		22.2 (19.5-25.8)
24-month outcomes						
Died	n (%)	157 (9.0)	461 (10.7)	258 (11.4)	100 (13.8)	16 (14.5)
LTFU	n (%)	331 (19.0)	643 (15.0)	251 (11.1)	105 (14.6)	23 (21.0)
Transferred out of care	n (%)	102 (5.9)	228 (5.3)	130 (5.7)	46 (6.4)	8 (7.3)
Alive and in care	n (%)	1148 (66.1)	2970 (69.0)	1629 (71.8)	470 (65.2)	63 (57.2)

ART, antiretroviral therapy; Hb, haemoglobin; LTFU, lost to follow-up; BMI, Body Mass Index

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Table 2

The Relation between Age and Mortality and Lost to Follow-up within 12- and 24-months on Antiretroviral Therapy at Themba Lethu Clinic, Johannesburg, South Africa (n=9139)

Death□	**12-Months**			**24-Months**		
	Deaths (n, %)	**Crude HR¥ (95% CI)**	**Adjusted€ HR¥ (95% CI)**	**Deaths (n, %)**	**Crude HR¥ (95% CI)**	**Adjusted€ HR¥ (95% CI)**
Age (yrs.)						
18-29.9	129 (7.4)	1.0	1.0	157 (9.0)	1.0	1.0
30-39.9	386 (9.0)	1.21 (0.99-1.48)	1.25 (1.02-1.54)	461 (10.7)	1.18 (0.99-1.42)	1.19 (0.99-1.44)
40-49.9	204 (9.0)	1.21 (0.97-1.51)	1.24 (0.98-1.57)	258 (11.4)	1.25 (1.03-1.53)	1.27 (1.04-1.57)
50-59.9	79 (11.0)	1.49 (1.13-1.98)	1.67 (1.24-2.23)	100 (13.9)	1.55 (1.21-2.00)	1.67 (1.29-2.18)
>60	12 (11.0)	1.54 (0.85-2.77)	1.54 (0.81-2.95)	16 (14.6)	1.70 (1.02-2.84)	1.74 (1.00-3.03)
Sex						
Female	446 (7.9)	1.0	1.0	546 (9.7)	1.0	1.0
Male	364 (10.4)	1.35 (1.17-1.55)	1.23 (1.06-1.42)	446 (12.8)	1.36 (1.20-1.54)	1.23 (1.08-1.41)
Baseline CD4 count (cells/mm^3)						
201-350	452 (14.2)	1.0	1.0	536 (16.8)	1.0	1.0
101-200	140 (8.0)	0.73 (0.56-0.96)	0.81 (0.60-1.11)	174 (9.9)	0.72 (0.57-0.92)	0.76 (0.58-0.99)
51-100	128 (4.7)	1.28 (0.98-1.67)	1.26 (0.92-1.72)	165 (6.0)	1.23 (0.97-1.55)	1.14 (0.87-1.50)
0-50	29 (5.2)	2.41 (1.92-3.02)	2.11 (1.60-2.79)	39 (7.0)	2.22 (1.82-2.71)	1.86 (1.46-2.36)
Baseline Haemoglobin						
≥10.0	446 (7.1)	1.0	1.0	559 (8.9)	1.0	1.0
≥10.0	310 (14.0)	2.16 (1.87-2.49)	1.71 (1.47-1.99)	369 (16.8)	2.1 (1.83-2.38)	1.69 (1.47-1.94)
Baseline BMI						
≥17.5	455 (6.7)	1.0	1.0	584 (8.6)	1.0	1.0
<17.5	355 (15.0)	2.45 (2.13-2.82)	1.94 (1.68-2.26)	408 (17.2)	2.24 (1.97-2.54)	1.78 (1.56-2.04)
Baseline WHO stage						
I/II	326 (6.8)	1.0	1.0	396 (8.2)	1.0	1.0
III/IV	484 (11.2)	1.70 (1.48-1.96)	1.21 (1.04-1.42)	596 (13.8)	1.73 (1.53-1.97)	1.24 (1.08-1.43)
Year initiatied ART						
2004	82 (6.8)	1.0	1.0	118 (9.8)	1.0	1.0

Death□	12-Months			24-Months		
	Deaths (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)	Deaths (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)
2005	156 (8.8)	1.32 (1.01-1.72)	1.17 (0.89-1.55)	209 (11.8)	1.24 (0.99-1.55)	1.12 (0.89-1.42)
2006	221 (9.9)	1.52 (1.18-1.96)	1.18 (0.90-1.54)	277 (12.4)	1.34 (1.08-1.67)	1.07 (0.86-1.35)
2007	209 (9.8)	1.53 (1.18-1.97)	1.32 (1.01-1.73)	241 (11.3)	1.24 (1.00-1.55)	1.10 (0.88-1.39)
2008	142 (7.9)	1.21 (0.92-1.58)	1.15 (0.87-1.52)	147 (8.2)	0.88 (0.69-1.12)	0.84 (0.66-1.08)

Loss to Follow-up§	12-Months			24-Months		
	Loss (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)	Loss (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)
Age (yrs.)						
18-29.9	214 (12.3)	1.0	1.0	331 (19.0)	1.0	1.0
30-39.9	448 (10.4)	0.85 (0.72-1.00)	0.84 (0.71-1.00)	643 (15.0)	0.78 (0.68-0.89)	0.77 (0.67-0.89)
40-49.9	243 (10.7)	0.86 (0.72-1.04)	0.84 (0.69-1.02)	351 (15.5)	0.81 (0.69-0.94)	0.78 (0.67-0.92)
50-59.9	72 (10.0)	0.83 (0.63-1.08)	0.81 (0.61-1.07)	105 (14.6)	0.78 (0.62-0.97)	0.75 (0.59-0.94)
>60	12 (10.9)	0.95 (0.53-1.70)	0.91 (0.49-1.67)	23 (21.0)	1.19 (0.78-1.81)	1.16 (0.75-1.80)
Sex						
Female	564 (10.0)	1.0	1.0	837 (14.8)	1.0	1.0
Male	425 (12.2)	1.25 (1.10-1.42)	1.32 (1.15-1.52)	616 (17.6)	1.24 (1.11-1.37)	1.29 (1.15-1.44)
Baseline CD4 count (cells/mm^3)						
201-350	376 (11.8)	1.0	1.0	520 (16.3)	1.0	1.0
101-200	171 (9.7)	0.85 (0.70-1.03)	0.87 (0.69-1.09)	264 (15.0)	0.93 (0.94-1.28)	1.01 (0.84-1.21)
51-100	276 (10.0)	0.85 (0.69-1.06)	0.87 (0.68-1.11)	433 (15.7)	0.93 (0.78-1.10)	0.93 (0.76-1.13)
0-50	57 (10.2)	1.12 (0.93-1.34)	1.03 (0.83-1.28)	86 (15.4)	1.10 (0.94-1.28)	0.93 (0.77-1.12)
Baseline Haemoglobin						
≥10.0	575 (9.1)	1.0	1.0	900 (14.3)	1.0	1.0
>10.0	328 (14.9)	1.84 (1.60-2.10)	1.76 (1.53-2.04)	437 (19.8)	1.60 (1.43-1.80)	1.53 (1.36-1.73)
Baseline BMI						
≥17.5	641 (9.5)	1.0	1.0	974 (14.4)	1.0	1.0
<17.5	348 (14.7)	1.76 (1.55-2.01)	1.56 (1.35-1.80)	479 (20.2)	1.64 (1.47-1.83)	1.51 (1.34-1.70)
Baseline WHO stage						
I/II	513 (10.7)	1.0	1.0	747 (15.6)	1.0	1.0

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Loss to Follow-up§	12-Months			24-Months		
	Loss (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)	Loss (n, %)	Crude HR¥ (95% CI)	Adjusted€ HR¥ (95% CI)
III/IV	476 (11.0)	1.08 (0.95-1.22)	0.94 (0.82-1.08)	706 (16.3)	1.10 (0.99-1.22)	0.99 (0.89-1.11)
Year initiatied ART						
2004	86 (7.1)	1.0	1.0	137 (11.4)	1.0	1.0
2005	180 (10.1)	1.47 (1.13-1.90)	1.45 (1.10-1.91)	270 (15.2)	1.40 (1.14-1.71)	1.41 (1.13-1.76)
2006	260 (11.7)	1.73 (1.36-2.12)	1.56 (1.20-2.04)	368 (15.2)	1.57 (1.29-1.91)	1.48 (1.20-1.84)
2007	260 (12.2)	1.85 (1.45-2.36)	1.79 (1.38-2.33)	375 (17.6)	1.71 (1.41-2.08)	1.73 (1.40-2.14)
2008	203 (11.3)	1.67 (1.30-2.15)	1.72 (1.32-2.26)	303 (16.9)	1.59 (1.30-1.94)	1.68 (1.35-2.08)

CI, confidence interval

¥Hazard ratio (HR) estimated from a Cox Proportional hazard model

€Models also adjusted for baseline ART regimen

□Death obtained from South African National Vital Registration System

§Lost to follow-up is defined as having missed a clinic appointment by at least 3 months after the scheduled visit date

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Table 3

The Relation between Age and CD4 Response and Virologic Suppression by 6- and 12-Months on Antiretroviral Therapy at Themba Lethu Clinic, Johannesburg, South Africa (n=9139)

Failure to Achieve CD4 Count Response[€]	**6-Months**			**12-Months**		
	Failure to achieve CD4 response (n, %)	**Crude RR**[£] **(95% CI)**	**Adjusted**[†] **RR**[£] **(95% CI)**	**Failure to achieve CD4 response (n, %)**	**Crude RR**[£] **(95% CI)**	**Adjusted**[†] **RR**[£] **(95% CI)**
Age (yrs.)						
18-29.9	223 (18.4)	1.0	1.0	79 (8.0)	1.0	1.0
30-39.9	671 (22.1)	1.20 (1.04-1.37)	1.14 (0.99-1.32)	279 (11.2)	1.39 (1.09-1.76)	1.36 (1.06-1.743)
40-49.9	393 (25.0)	1.35 (1.17-1.56)	1.23 (1.06-1.43)	153 (11.2)	1.50 (1.16-1.94)	1.35 (1.03-1.78)
50-59.9	150 (29.9)	1.62 (1.35-1.94)	1.43 (1.18-1.72)	64 (15.1)	1.96 (1.44-2.67)	1.66 (1.20-2.29)
>60	27 (35.5)	1.93 (1.39-2.67)	1.44 (1.01-2.06)	17 (27.9)	3.49 (2.21-5.50)	2.82 (1.78-4.46)
Baseline CD4 Count (cells/mm^3)						
0-50	405 (18.7)	1.0	1.0	86 (4.8)	1.0	1.0
51-100	270 (20.6)	1.10 (0.96-1.26)	1.10 (0.96-1.27)	109 (10.0)	2.06 (1.57-2.71)	2.13 (1.61-2.82)
101-200	580 (27.0)	1.45 (1.29-1.62)	1.46 (1.31-1.64)	296 (16.8)	3.49 (2.76-4.39)	3.76 (2.96-4.79)
201-350	145 (33.5)	1.79 (1.53-2.10)	1.77 (1.50-2.09)	72 (20.8)	4.29 (3.21-5.74)	4.67 (3.43-6.34)
Baseline Regimen						
d4T-3TC-EFV	1309 (22.9)	1.0	1.0	545 (11.6)	1.0	1.0
d4T-3TC-NVP	95 (19.5)	0.85 (0.71-1.03)	0.94 (0.77-1.13)	27 (6.7)	0.57 (0.39-0.83)	0.66 (0.46-0.96)
AZT-3TC-NVP / EFV	60 (31.3)	1.37 (1.10-1.70)	1.22 (0.98-1.51)	20 (12.6)	1.08 (0.71-1.64)	0.92 (0.60-1.41)

Failure to Achieve Viral Load Suppression[¥]	**6-Months**			**12-Months**		
	Failure to achieve viral load suppression (n, %)	**Crude RR**[£] **(95% CI)**	**Adjusted**[†] **RR**[£] **(95% CI)**	**Failure to achieve viral load suppression (n, %)**	**Crude RR**[£] **(95% CI)**	**Adjusted**[†] **RR**[£] **(95% CI)**
Age (yrs.)						
18-29.9	122 (10.7)	1.0	1.0	86 (9.6)	1.0	1.0
30-39.9	256 (9.1)	0.85 (0.69-1.04)	0.87 (0.70-1.09)	204 (8.9)	0.92 (0.72-1.17)	0.93 (0.72-1.20)
40-49.9	122 (8.1)	0.76 (0.60-0.96)	0.75 (0.58-0.98)	109 (9.6)	1.00 (0.76-1.30)	0.90 (0.67-1.21)

Failure to Achieve Viral Load Suppression[¥]	6-Months			12-Months		
	Failure to achieve viral load suppression (n, %)	Crude RR[£] (95% CI)	Adjusted[†] RR[£] (95% CI)	Failure to achieve viral load suppression (n, %)	Crude RR[£] (95% CI)	Adjusted[†] RR[£] (95% CI)
50-59.9	36 (7.7)	0.71 (0.50-1.02)	0.80 (0.55-1.17)	34 (9.4)	0.98 (0.67-1.43)	1.06 (0.71-1.58)
>60	6 (8.7)	0.81 (0.37-1.77)	0.99 (0.45-2.17)	3 (5.8)	0.60 (0.20-1.83)	0.67 (0.22-2.05)
Baseline CD4 Count (cells/mm^3)						
0-50	182 (9.2)	1.0	1.0	151 (9.8)	1.0	1.0
51-100	103 (8.7)	0.95 (0.76-1.20)	0.94 (0.74-1.19)	90 (9.8)	1.00 (0.78-1.28)	1.01 (0.79-1.04)
101-200	171 (8.8)	0.96 (0.79-1.17)	0.96 (0.78-1.18)	123 (8.0)	0.82 (0.65-1.02)	0.82 (0.65-1.32)
201-350	25 (6.6)	0.72 (0.48-1.07)	0.75 (0.50-1.13)	24 (7.9)	0.81 (0.53-1.22)	0.86 (0.57-1.30)
Baseline Regimen						
d4T-3TC-EFV	464 (8.7)	1.0	1.0	371 (8.8)	1.0	1.0
d4T-3TC-NVP	55 (12.1)	1.40 (1.08-1.82)	1.42 (1.06-1.89)	50 (13.7)	1.56 (1.19-2.06)	1.53 (1.21-2.10)
AZT-3TC-NVP / AZT-3TC-EFV	23 (12.9)	1.48 (1.00-2.19)	1.34 (0.85-2.12)	15 (10.5)	1.20 (0.74-1.95)	1.10 (0.64-1.92)

[£] Relative risk (RR) estimated from a log-binomial regression model

[†] Models adjusted for sex, baseline haemoglobin, baseline WHO stage and baseline BMI

[€] Failure to achieve a CD4 response defined as an increase of ≥50 cells/mm^3

[¥] Failure to achieve VL suppression defined as not reaching a viral load <400 copies/ml VL, viral load; CI, confidence interval