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HIV and aging: insights from the Asia Pacific HIV Observational Database (APHOD)

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Abstract

Background—The proportion of people living with HIV/AIDS in the ageing population (>50 years) is increasing. We aim to explore the relationship between older age and treatment outcomes in HIV-positive persons from the Asia-Pacific region.

Methods—Patients from the Australian HIV Observational Database (AHOD) and the TREAT Asia HIV Observational Database (TAHOD) were included in the analysis. We used survival methods to assess the association between older age and all-cause mortality, as well as time-to treatment modification. We used regression analyses to evaluate changes in CD4 counts after combination antiretroviral therapy (cART) initiation and determined the odds of detectable viral load, up to 24 months of treatment.

Results—A total of 7142 patients were included in these analyses (60% TAHOD, 40% AHOD), of which, 25% were >50 years old. In multivariable analyses those aged >50 were at least twice as likely to die as those aged 30-39 years [HR (50-59 years): 2.27, 95% CI: 1.34-3.83; HR (>60years) 4.28, 95% CI: 2.42-7.55]. The effect of older age on CD4 count changes was insignificant (p-trend=0.06). The odds of detectable viral load after cART initiation decreased with age (p-trend=<0.0001). The effect of older age on time-to first treatment modification was insignificant (p-trend=0.21). We found no statistically significant differences in outcomes between AHOD and TAHOD participants for all endpoints examined.

Conclusion—The associations between older age and typical patient outcomes in HIV-positive patients from the Asia-Pacific region are similar in AHOD and TAHOD. Our data indicate that ‘age-effects’ traverse the resource-rich and resource-limited divide and indicate that future ageing-related findings might be applicable to each setting.

Keywords

HIV infection; ageing; Asia Pacific; outcomes; older patients; combination antiretroviral treatment

Introduction

After the scale-up of combination antiretroviral therapy (cART) in both resource-rich and resource-limited countries, most treated HIV-positive patients experience longer survival [1]. As the role out of frequent HIV-testing is expanded, an increasing proportion of new HIV diagnoses are found in older people [2,3]. Reasons for increases in new infections in older populations are multifactorial. Although HIV is transmitted at all ages, older individuals may be less inclined to be offered or request HIV testing as a consequence of both provider and patient perception of lack of risk [2]. In addition to HIV-positive patients surviving longer and a higher rate of diagnoses made in older individuals, there are now many older persons living with HIV/AIDS [4,5].

It has been suggested that HIV infection is associated with both physical and immunological changes commonly found in HIV-negative ageing populations. Desquilbet et al [6] reported that HIV-1 infection was associated with earlier occurrence of frailty (physical shrinking; unintentional weight loss; self-reported exhaustion; low physical activity; slowness; weakness of grip strength) and risk of exhibiting ‘frailty’ increased with duration of HIV infection. Exposure to HIV (including viral suppression) and long-term cART has been suggested to accelerate the body's natural ageing processes as a result of persistent immune activation and treatment induced pro-inflammatory effects leading to premature immunosenescence (ageing of the immune system) [7-12]. Furthermore, despite the clear success of cART, HIV-positive people appear to have an increased risk of serious ageing-related diseases including cardiovascular, liver and kidney disease, malignancies and bone disorders [13,14].

The additive effects of immunological changes associated with natural ageing and those resulting from HIV infection may affect the response to cART in ageing populations. Previous studies have shown that older populations have slower increases in CD4 after starting cART [15-18] even though older HIV-positive patients are more likely to achieve and maintain HIV-RNA viral load suppression compared to younger patients [16-21]. The population level response to cART and subsequent adherence and access to continual cART influence patterns of all-cause mortality. While it is expected that older aged HIV-positive persons would have a higher risk of mortality compared to younger population, comparing against general population level mortality rates, a notable excess risk differential exists across all age groups [22] [23]. There are minimal data published on directly comparing ageing associations for typical HIV treatment outcomes in resource-rich and resource-limited settings.

The objective of this analysis is to explore the relationship between older age and typical HIV treatment related outcomes. We aim to examine the associations between- older age and all-cause mortality; older age and mean CD4 cell count change in response to antiretroviral therapy; older age and the odds of detectable HIV-RNA viral load; older age and time-to first major treatment modification. The primary aim of this study is to establish and compare the patterns of older age associations in a cohort of patients from both resource-rich and resource-limited countries.

Methodology

Study Population

The Asia-Pacific HIV Observational Database (APHOD) is part of the International Epidemiological Databases Evaluating AIDS (IeDEA) collaboration and consists of two adult cohorts, the Australian HIV Observational Database (AHOD), the TREAT Asia HIV Observational Database (TAHOD), as well as one paediatric cohort, the TREAT Asia Paediatric HIV Observational Database (TApHOD). This study includes the AHOD and TAHOD adult cohorts only. AHOD data are collected from 27 clinical sites throughout Australia, including hospitals, sexual health clinics and clinics of general practitioners. Prospective data collection commenced in 1999 and retrospective data are provided where available. Patients written and informed consent to participate is obtained at time of enrollment. TAHOD data are primarily collected from 17 tertiary clinical sites throughout Asia. Prospective data collection commenced in 2003 and retrospective data are provided where available. Patients written and informed consent is obtained at enrollment in sites where it is required by the local ethics committee, otherwise data at sites are collected anonymously. Ethics approval for APHOD was granted to all participating sites by relevant institutional review boards. All APHOD study procedures were developed in accordance with the revised 1975 Helsinki Declaration.

Twice-annually (March, September) data for AHOD and TAHOD are collected on a core set of demographic and clinical variables and transferred electronically to the Kirby Institute, UNSW Australia, Sydney, Australia. Detailed description of each cohort has been previously described elsewhere, and data are subjected to quality control and quality assurance standardized procedures [24,25]. All patients with at least one follow-up visit and who were recruited up to March 2010 for AHOD and September 2009 for TAHOD were included in the analysis. We further restricted our analysis population to patients initiating cART without any prior exposure to ART (treatment naïve only).

Statistical Analysis

We defined an older patient as calendar year age >50 years old. We tabulated demographics and clinical characteristics of the study population stratified by age groups- younger/older.

Cox proportional hazards (PH) models adjusted for fixed and time-updated covariates were used to estimate the hazard ratio (HR) of older age and the association with all-cause mortality (composite endpoint of AIDS-related and non-AIDS related deaths) and separately, the associate of older age with time-to first major treatment modification. We

defined a treatment modification as a change from the original regimen of at least two drugs or by the addition (or subtraction) of a new class of antiretroviral. Treatment modifications due to any reason were included as endpoints, including modification due to toxicity/side-effects, virological failure, patient or physician decision, and unknown. Follow-up time was measured from the date of cART initiation or cohort enrollment for the mortality endpoint, whichever came later, and time-to first treatment modification was measured from initiation of cART. Patients were censored if not seen at the clinic for 12 months prior to the site administration censoring date of 30th September 2009 for TAHOD, or 31st March 2010 for AHOD.

Absolute differences in CD4 cell count (cells/ μ L) compared with pre-cART CD4 count levels were examined at 6, 12, 18 and 24 months duration of cART. We used Generalised Estimating Equations (GEE), assuming an exchangeable correlation structure to account for within patient variation of the data. A Logistic GEE with an exchangeable correlation structure was used to estimate the odds ratios (OR) associated with older age and the probability of having a detectable viral load (defined as plasma HIV-RNA >400 copies/ml) at 6, 12, 18 and 24 months duration of ART. We conducted sensitivity analyses to examine the robustness of our results. Based on previous analyses, we examined different model specifications for our CD4 count modeling [26-28] and evaluated the influence of reduced viral load testing in some participating TAHOD clinics by restricting the data to complete-case analyses [29].

Multivariable models (both Cox proportional hazards and GEE) were adjusted for sex; likely mode of HIV exposure (homosexual, heterosexual, injecting drug user, other, missing); AIDS illness (Yes, No); cohort (AHOD, TAHOD); calendar year (<1999, 1999-2001, 2002-2004, 2005-2007, 2008-2010); and if appropriate time-updated CD4 count (less than 50, 50-99, 100-199, 200-349, 350-500, 500+, missing); viral load (HIV RNA <400, RNA >400 copies/ml, missing) and duration of cART (6, 12, 18, 24 months). Multivariable models covariates were added to the model *a priori* and no form of model selection was considered. For each endpoint an interaction term between age and cohort was fitted to statistically assess any significant differences in cohort ageing effects. We assumed “intention-to-continue-treatment” and ignored any changes, interruptions or the termination of treatment after initiation of cART. All statistical analyses were computed using SAS software, Version 9.1.3 of the SAS System for Windows.

Results

Clinical and demographic characteristics

The proportion of patients under the age of fifty years was 75% in the combined cohort, or 60% and 84% in AHOD and TAHOD respectively (Table 1a). Of the younger population, approximately 90% (N=4725) were aged between 30-49 and the remaining 10% (N=608) were under the age of 30. In the older population, 67% were aged 50-59 (N=1 210) and 33% (N=599) were aged 60 years and over. The older population predominately consisted of AHOD patients (62%). Males represented the majority in both the younger and older populations (77% and 89%, respectively). The predominant likely mode of HIV exposure was homosexual contact in AHOD participants, and heterosexual contact in the TAHOD

participants. The proportions of hepatitis B, or hepatitis C co-infection were similar in both the older and younger groups in both AHOD and TAHOD. Older patients had a longer time since HIV diagnosis than younger patients and similarly, the average duration of cART was greater in the older group (Table 1b). The proportion of patients on their 4th (or more) cART regimen was higher in older patients compared to younger patients (36% vs. 15% respectively). The anchor agents used in the patient's most recent cART regimen for older and younger patients were proportionally similar. Immunological differences determined from the patients most recent clinical visit were similar in older and younger patients, and the proportion of patients with detectable HIV RNA viral load was lower in the older population (10% vs. 20% in the younger group).

All-cause Mortality

Risk of all-cause mortality increased with age in both univariate and multivariate Cox models (Table 2). Relative to persons aged 30-39 years old, patients aged 50-59 years had a 2-fold increase (95% CI: 1.4-3.8) risk of all-cause mortality and patient's aged 60+ had a 4-fold increase (95% CI: 2.4-7.5) in risk of all-cause mortality. Within each age stratum, there were different proportions of IDU mode of HIV exposure potentially confounding our results. To adjust for this, we fitted an interaction between younger patients and IDU mode of HIV exposure and we found the interaction term to be insignificant (p-value=0.38, HR not shown). We found no differences for the association of older age and risk of all-cause mortality between the two cohorts (Figure 1). Cox Model assumptions, including the validity of proportional hazards were not violated.

Immunological Responses

CD4 cell count responses to antiretroviral treatment varied over time and were largely determined by CD4 cell count at cART initiation (Table 2). The effect of older age on CD4 cell response was statistically insignificant (p-trend=0.06). However, patient's aged 60+ had statistically poorer immunological responses. Patients in this age group had a mean difference in absolute CD4 count gain of -45 cells/ μ l (95% CI: -75 to -14 cells/microliter) relative to 30-39 year olds patients. The interaction term between older age and cohort was statistically insignificant (p-value=0.72) and sensitivity analyses showed the estimated age effects were robust under different model specifications adjusting for time and pre-cART CD4 cell count (data not shown).

Detectable Viral Load

The odds of detectable viral load were associated with age (Table 2). Older age groups relative to the reference group (30-39 years) had significantly lower odds of detectable viral load. In the multivariable model, 40-49 years old patients had a relative Odds Ratio (OR) of 0.69 (95% CI: 0.54-0.89), and patients aged 50-59 and 60+ years had respectively an OR of 0.53 (95% CI: 0.36-0.78) and 0.55 (95% CI: 0.31-0.97). Patients <30 years old had an increased OR of detectable viral load relative to patients aged 30-39 years. We found no differences in the measured age association across the two cohorts, AHOD and TAHOD (Figure 2). Sensitivity analyses were performed to assess the impact of patients who were lost to follow-up and missing records. Resulting age associations were qualitatively similar.

Time to cART Regimen Change

We found no significant age effect for the time-to major treatment modification (across all competing risks of switching), $p=0.21$ (Table 2). The interaction term between age and cohort was insignificant. A strong cohort effect was identified. TAHOD patients were half as likely, relative to AHOD, to change treatment (HR=0.59; 95% CI: 0.5-0.64) during our observed study period.

Discussion

In this study we found that ageing in HIV-positive APHOD patients was statistically significantly associated with increased all-cause mortality and a decreased likelihood of detectable viral load after cART initiation. Ageing was not significantly associated with a reduced response in CD4 counts after treatment initiation, except in patients older than 60 years old. We found that age was not associated with time-to first major modification of cART, and importantly, we show that the patterns of the association between age and all-cause mortality were consistent in HIV-patients from both resource-rich and resource-limited countries.

Many studies have shown an association between older age and increased risk of all-cause mortality [5,16,17,30,34]. Our results are consistent with these ageing trends in terms of magnitude and direction of risk. Additionally, our results are consistent with previous reports that have shown that older HIV populations initiating cART have higher odds of maintaining an undetectable HIV-RNA viral load during follow-up [16-21]. In a prospective cohort study conducted by Nogueras et al., it was hypothesised that this observation is related to better demonstrated treatment adherence in older patients, whom may have more stable lifestyles than younger patients [16]. Others have shown that increases in CD4 cell count following initiation of cART may be blunted in older patients [15-18]. Our data support this finding, though primarily in older age patients (>60 years old). However the clinical significance of this finding and how it translates into an risk of all-cause mortality remains unclear. The rates of time-to first major modification of cART are similar in older and younger HIV-positive patients which is consistent with other studies that evaluated predictors of early cART modification [20,29,31]. Older age is generally not associated with treatment modification.

In this study, our key finding was the lack of statistically significant different patterns in the association between older age and HIV related treatment outcomes in resource-rich (AHOD) and resource-limited (TAHOD) countries. The patient demographics; clinical characteristics; availability of cART; clinical care setting; and availability of medical resources in AHOD and TAHOD are vastly different [32,33]. Nevertheless, we report markedly similar ageing associations for all typical HIV-related treatment outcomes and suggest that some results or findings from future ageing studies might be applicable to both resource-rich and resource-limited settings.

There are limitations to our analyses. We do not report any associations between older age and the risk of serious non-AIDS events (SNE) or other known biomarkers associated with ageing related morbidity (CD4/CD8 ratios, d-dimer, IL-6, etc). We do not collect these data routinely in AHOD and in TAHOD, however collection of SNE's data has recently

commenced in TAHOD. The two cohorts are substantially different and we have attempted to adjusted for this by fitting an interaction terms in all of our models. However, within TAHOD there are many different ethnicities, from low, middle and high income countries, which might confound our results. Previous APHOD studies that specifically aimed to compare outcomes between high- and low-income countries or between ethnicities found little difference [26,29,34-37].

In conclusion, this study on HIV and ageing in the Asia-Pacific region has shown that older patients on cART maintained better virological control than younger patients. Older patients had marginally poorer CD4 cell response and a two-fold higher risk of all-cause mortality. We found no differences in the time-to first major modification of cART. Importantly, we did not find any significant difference in the ageing associations of typical HIV-related outcomes between a resource-rich and a predominately resource-limited cohort. As the number of ageing HIV-positive patients increases in the coming years, many will experience typical ageing related morbidity, perhaps earlier and further complicated by their HIV infection. The general burden of disease in the ageing HIV-population and the affect on financial resources is yet to be determined and warrants further investigation.

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Figure 1. The association of the hazard ratio for all cause mortality with age stratified by cohort AHOD, Australian HIV Observational Database; CI confidence interval; TAHOD, TREAT Asia HIV Observational Database.

Figure 2. Association of odds ratio of detectable HIV RNA viral load with age stratified by cohort

AHOD, Australian HIV Observational Database; CI, confidence interval; TAHOD, TREAT Asia Observational Database.

Table 1a
Characteristics of older and younger HIV-positive patients in APHOD, AHOD and TAHOD

	APHOD		AHOD		TAHOD	
	<50 years	50 years	<50 years	50 years	<50 years	50 years
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	5333 (75)	1809 (25)	1697 (60)	1127 (40)	3636 (84)	682 (16)
Sex						
Female	1240 (23)	192 (11)	130 (8)	37 (3)	1110 (31)	155 (23)
Male	4093 (77)	1617 (89)	1567 (92)	1090 (97)	2526 (69)	527 (77)
Likely mode of HIV exposure						
Unknown	61 (1)	10 (1)	11 (1)	7 (1)	50 (1)	3 (0)
Homosexual contact	1912 (36)	1001 (55)	1219 (72)	879 (78)	693 (19)	122 (18)
Injecting drug user	390 (7)	41 (2)	134 (8)	31 (3)	256 (7)	10 (1)
Heterosexual contact	2544 (48)	581 (32)	170 (10)	96 (9)	2374 (65)	485 (71)
Other	426 (8)	176 (10)	163 (10)	114 (10)	263 (7)	62 (9)
Ethnicity						
Caucasian	1697 (32)	1127 (62)	1697 (100)	1127 (100)	-	-
Chinese	953 (18)	270 (15)	-	-	953 (26)	270 (40)
Indian	545 (10)	57 (3)	-	-	545 (15)	57 (8)
Thai	871 (16)	149 (8)	-	-	871 (24)	149 (22)
Other	1267 (24)	206 (11)	-	-	1267 (35)	206 (30)
Age (years)[†]						
Less 30	608 (11)	-	87 (5)	-	521 (14)	-
30 - 39	2256 (42)	-	544 (32)	-	1712 (47)	-
40 - 49	2469 (46)	-	1066 (63)	-	1403 (39)	-
50 - 59	-	1210 (67)	-	735 (65)	-	475 (70)
60+	-	599 (33)	-	392 (35)	-	207 (30)
Hepatitis B						
Positive	314 (8)	97 (7)	87 (6)	45 (5)	227 (10)	52 (11)
Negative	3405 (92)	1354 (93)	1286 (94)	940 (95)	2119 (90)	414 (89)
Not Tested	1614	358	324	142	1290	216

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	TAHOD		AHOD		APHOD	
	50 years	>50 years	50 years	>50 years	50 years	>50 years
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hepatitis C						
Positive	32 (8)	282 (14)	84 (8)	216 (14)	116 (8)	498 (14)
Negative	394 (92)	1758 (86)	931 (92)	1277 (86)	1325 (92)	3035 (86)
Not Tested	256	1596	112	204	368	1800

/ At patients' most recent clinic visit.

Table 1b
Clinical characteristics of older and younger HIV-positive patients in APHOD, AHOD and TAHOD

	<u>APHOD</u>		<u>AHOD</u>		<u>TAHOD</u>	
	<50 years	50 years	<50 years	50 years	<50 years	50 years
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Time since first positive HIV test (years)						
Mean (std)	8 (5)	12 (7)	12 (6)	15 (7)	6 (4)	7 (4)
Median (IQR)	6 (4-11)	11 (6-18)	11 (7-16)	15 (0-21)	5 (3-8)	7 (4-9)
AIDS Illness Status¹						
Yes	2577 (48)	735 (41)	339 (20)	298 (26)	2238 (62)	437 (64)
No	2756 (52)	1074 (59)	1358 (80)	829 (74)	1398 (38)	245 (36)
Treatment Regimen Number³						
Naïve	806 (15)	130 (7)	260 (15)	78 (7)	546 (15)	52 (8)
1st	1653 (31)	353 (20)	341 (20)	148 (13)	1312 (36)	205 (30)
2nd	1329 (25)	369 (20)	327 (19)	175 (16)	1002 (28)	194 (28)
3rd	719 (13)	308 (17)	247 (15)	179 (16)	472 (13)	129 (19)
4th plus	826 (15)	649 (36)	522 (31)	547 (49)	304 (8)	102 (15)
Duration of cART (months)⁴						
Mean (std)	57 (37)	82 (42)	68 (44)	91 (44)	51 (32)	66 (34)
Median (IQR)	52 (27-79)	80 (48-118)	63 (30-104)	97 (55-131)	49 (26-73)	66 (41-86)
Treatment Regimen Type⁵						
Off treatment/Naïve	667 (13)	82 (5)	213 (13)	48 (4)	454 (12)	34 (5)
3+ II, ±NRTI, ±NNRTI, ±PI	87 (2)	123 (7)	81 (5)	118 (10)	6 (0)	5 (1)
3+ NNRTI+PI, ±NRTI	115 (2)	87 (5)	91 (5)	77 (7)	24 (1)	10 (1)
3+ NRTI+NNRTI	2876 (54)	809 (45)	606 (36)	409 (36)	2270 (62)	400 (59)
3+ NRTI+PI	1198 (22)	490 (27)	496 (29)	302 (27)	702 (19)	188 (28)
3+ NRTI	71 (1)	37 (2)	55 (3)	31 (3)	16 (0)	6 (1)
Mono/Duo/Other	319 (6)	181 (10)	155 (9)	142 (12)	164 (5)	39 (6)
CD4 cell count (cells/μL)²						
0 – 50	147 (3)	28 (2)	44 (3)	13 (1)	103 (3)	15 (2)

	<u>APHOD</u>		<u>AHOD</u>		<u>TAHOD</u>	
	<50 years	50 years	<50 years	50 years	<50 years	50 years
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
50 – 100	109 (2)	32 (2)	22 (1)	17 (2)	87 (2)	15 (2)
100 – 200	334 (6)	105 (6)	55 (3)	44 (4)	279 (8)	61 (9)
200 – 350	854 (16)	301 (17)	187 (11)	148 (13)	667 (18)	153 (22)
>350	2813 (53)	1085 (60)	1100 (65)	768 (68)	1713 (47)	317 (46)
Missing	1076 (20)	258 (14)	289 (17)	137 (12)	787 (22)	121 (18)
HIV RNA viral load (copies/ml)²						
400	2339 (44)	1231 (68)	1010 (60)	865 (77)	1329 (37)	366 (54)
>400	639 (12)	142 (8)	380 (22)	108 (10)	259 (7)	34 (5)
Missing	2355 (44)	436 (24)	307 (18)	154 (14)	2048 (56)	282 (41)

¹ At patients' most recent clinical visit.

² Measurement closest to the most recent clinic visit date. Missing assigned if last test date is outside a 6-month window.

³ Treatment is defined as duration of treatment >14 days, number of ARVs ≥ 3 and start of treatment >1996.

⁴ Time receiving cART (in months), does not include structured treatment breaks or time off treatment.

⁵ Based on the last treatment record available for patient.

Table 2
Age associations of all-cause mortality, time-to first treatment modification, mean change CD4 cell count response, and odds of detectable HIV-RNA viral load

Age Association	Univariate Model			Multivariable Model ¹		
	Estimate	p-value	global p-value	Estimate	p-values	global p-value
All-cause mortality (Hazard Ratio)						
<30	1.55 (0.81 to 2.96)	0.19	0.001	1.58 (0.81 to 3.06)	0.18	<0.0001
30-39 (reference)	1.00	-	-	1.00	-	-
40-49	1.50 (0.99 to 2.28)	0.06		1.61 (1.05 to 2.45)	0.03	
50-59	1.75 (1.05 to 2.93)	0.03		2.27 (1.34 to 3.83)	<0.0001	
60	3.17 (1.84 to 5.47)	<0.0001		4.28 (2.42 to 7.55)	<0.0001	
Mean change CD4 cell count (absolute mean difference)						
<30	-16 (-35 to 4)	0.11	0.3	-5 (-23 to 13)	0.57	0.06
30-39 (reference)	0.0	-	-	0.0	-	-
40-49	-7 (-25 to 11)	0.46		-13 (-31 to 4)	0.14	
50-59	-9 (-33 to 15)	0.45		-16 (-39 to 7)	0.18	
60	-30 (-61 to 2)	0.07		-45 (-75 to -14)	<0.0001	
Probability of detectable viral load (Odds Ratio)						
<30	1.42 (1.12 to 1.8)	0.01	<0.0001	1.36 (1.07 to 1.73)	0.01	<0.0001
30-39 (reference)	1.00	-	-	1.00	-	-
40-49	0.73 (0.57 to 0.93)	0.01		0.69 (0.54 to 0.89)	<0.0001	
50-59	0.61 (0.42 to 0.88)	<0.0001		0.53 (0.36 to 0.78)	<0.0001	
60	0.52 (0.29 to 0.91)	0.05		0.55 (0.31 to 0.97)	0.04	
Time until treatment change (Hazard Ratio)						
<30	0.89 (0.77 to 1.03)	0.13	0.55	0.89 (0.77 to 1.03)	0.13	0.55
30-39 (reference)	1.00	-	-	1.00	-	-
40-49	0.99 (0.89 to 1.1)	0.87		0.99 (0.89 to 1.1)	0.87	
50-59	1.02 (0.88 to 1.17)	0.82		1.02 (0.88 to 1.17)	0.82	
60	1.06 (0.86 to 1.3)	0.61		1.06 (0.86 to 1.3)	0.61	

¹ Multivariable model adjusted for sex, cohort, HIV exposure, AIDS illness, calendar year, duration of cART, and where appropriate time-updated CD4 cell count, time-updated HIV-RNA viral load.