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Changing predictors of mortality over time from cART start: implications for care

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Abstract

Objective—To determine predictors of mortality and changes in those predictors over time on combination antiretroviral therapy (cART) in South Africa.

Design—A cohort study.

Methods—Using routine clinic data with up to 4 years follow-up after ART initiation and with death ascertainment from a national vital statistics register, we used proportional hazards modeling to assess baseline and time-updated predictors of mortality, and changes in strength of those predictors over time on cART. Furthermore, we compared CD4 count among individuals who died by duration on cART.

Results—15,060 subjects (64% men, median CD4 count 127 cells/mm³) started antiretroviral therapy between January 2003 and January 2008. Over a median follow-up of 1.8 years, 2,658 subjects died. The baseline characteristics of WHO stage, haemoglobin, CD4 count, HIV RNA level, and symptoms were all associated with mortality during the first 12 months of cART but lost association thereafter. However time updated factors of CD4 count, body mass index, symptoms, anemia, and HIV RNA suppression remained strong predictors of death. Most recent CD4 count prior to death rose from 71 during the first 3 months of cART to 175 cells/mm³ after >3 years of cART.

Conclusion—Over 4 years of cART, risk of death declined and associations with mortality changed. An increase in CD4 count at death and changing associations with mortality may suggest a shift in causes of death, possibly from opportunistic infections to other infections and chronic illnesses.

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Keywords

mortality; HIV; resource limited setting; Africa; antiretroviral therapy; proportional hazards

Background

HIV-related illness is the leading cause of death in southern Africa ¹⁻³. Combination antiretroviral therapy (cART) improves immune function and decreases the risk of opportunistic illness and death ⁴⁻⁶. However, early mortality after starting cART is high. In addition, the mortality among individuals on cART remains elevated above the population level even after years on cART ⁷.

In industrialized countries, with the wider use of cART, causes of death among people living with HIV have changed over time. While opportunistic illnesses remain an important cause of death, non-AIDS defining malignancies, liver disease, and cardiovascular disease have increased as causes of death among individuals receiving cART ⁸⁻¹³. Risk factors for death have also changed over time. For example, as fewer individuals die of opportunistic illnesses, co-infection with chronic viral hepatitis has emerged as an important risk factor for premature death ^{8;14-17}.

In resource limited settings, post-mortem studies performed in cART naïve individuals and individuals who died early after starting cART have demonstrated that opportunistic infections are the leading cause of death among those individuals ¹⁸⁻²⁰. Consistent with the findings from these post-mortem studies, low CD4 count, low weight, and anemia, are risk factors for mortality during this period ^{7;21-34}. With a growing number of individuals in resource limited countries now on long-term cART, an understanding of the longer term benefits, risks, and complications during cART is needed. However, there are few descriptions of either the cause of death or the associated predictors of death after 12 or more months of continuous cART. Assessing changes in the strength of association of potential risk factors by time since cART initiation may provide insight into changing patterns of mortality over time. Understanding these predictors will be valuable for targeting interventions to reduce mortality among patients on chronic cART. Using a large cohort of patients receiving cART in South Africa we sought to determine predictors of mortality and changes in these predictors over time.

Methods

Patients and Programmes

The study cohort was recruited from 279 (214 community and 65 workplace-based) ART clinics. Patients in this study were enrolled in a multisite community and workplace-based HIV management programme in South Africa and met the following criteria: 1) ART naïve and initiated cART (2 nucleoside reverse transcriptase inhibitors plus a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor) between January 2003 and January 2008, 2) 18 years old, and 3) had recorded national identification numbers or other identifiers to link to vital status registers. Subjects from the workplace-based clinics started cART from January 2003 onwards while subjects in the community-based clinics started

cART from January 2004 onwards. The number of patients meeting inclusion criteria from a given clinic ranged between 1 and 1637. For the workplace-based clinics, cART eligibility was based on CD4 count <250 cells/mm³; WHO stage 3 and CD4 count <350 cells/mm³; or WHO stage 4 condition. For the community-based clinics, cART eligibility was based on CD4 count <200 cells/mm³ or WHO stage 4 condition. The first-line regimen was a combination of either zidovudine or stavudine, lamivudine, and either efavirenz or nevirapine. All clinics used similar monitoring schedules with HIV RNA and CD4 count determined before cART initiation, after six weeks on cART, and every six months.

Death Ascertainment

We used three methods of ascertaining death: 1) deregistration forms in which clinicians used information reported by patients, family members, hospitals, and community members to record reasons for discontinuation of cART, including death, 2) in the workplace programmes, human resources data that identified workers who either died or were separated from employment, and 3) linkage to the South African vital statistics registry. We counted a death recorded via any of these methods. Workers who were terminally ill and were unable to report to work for 3 to 6 months and were not expected to return to work within another 12 months were medically separated from employment and were referred to community clinics for care. To minimize under-ascertainment of death as a result of work separation of terminally ill individuals, we included medical separations as a death surrogate for a combined mortality endpoint. We have previously used this technique to minimize under ascertainment³⁵.

Loss to follow-up was defined as the absence of any further clinic visits for >12 months after the last documented visit.

Exposure Definitions

Cotrimoxazole—Cotrimoxazole use was defined as receiving cotrimoxazole preventive therapy (sulfamethoxazole 800mg and trimethoprim 160mg daily) within 30 days of cART initiation. We used this definition because of uncertainty regarding discontinuation dates.

HIV RNA suppression—This was defined as an HIV RNA <400 c/mL. This level was used to maintain consistency with previous reports and to avoid including viral blips as non-suppression. We further stratified by <6 months on cART, as many of the subjects with a 6 week HIV RNA assay had an appropriate response but not complete suppression by that time period. Thus we had a four level variable: (1) <6 months cART, (2) 6 months cART and HIV RNA <400 c/mL, (3) 6 months cART and HIV RNA ≥ 400 c/mL, and (4) 6 months cART and missing data.

TB symptoms—The following symptoms were part of the routine patient visit form as self-reported dichotomous variables: fever, cough, sputum production, weight loss, and night sweats. Any further questioning by a health care provider regarding nature or duration of symptoms was recorded separately and not captured into the programme monitoring and evaluation database. We created a stratum for missed visits if >3 months from the prior visit.

Characteristics at cART start—We evaluated the following variables measured at the start of cART: sex, age, body mass index (BMI), haemoglobin, $\log_{10}$ HIV RNA, absolute CD4 count, WHO clinical stage, and TB symptoms.

Time-updated characteristics—Characteristics with repeated measures, such as TB symptoms, CD4 count, haemoglobin, body mass index (BMI), and HIV RNA suppression were analyzed as time updated variables, only contributing to a three month time interval during which they were obtained and the next time interval, if carried forward.

Laboratory

HIV RNA was assayed by polymerase chain reaction (Amplicor HIV-1 Monitor Test, Roche Diagnostics, Nutley, New Jersey, USA) or branched chain DNA analysis (Bayer Versant, New York, USA). Absolute CD4 count was assayed by flow cytometry (Becton Dickinson, Mountain View, California, USA). All laboratory tests were performed at commercial certified laboratories in South Africa.

Statistical Analysis

Subjects entered evaluation at the time of cART initiation and exited analysis March 2010 or after 48 months of cART, loss to follow-up, recorded discontinuation of cART, transfer to another cART programme, or death. Mortality rates by duration of cART were described. Cox proportional hazards regression was used to assess predictors of the combined mortality endpoint. We assessed for effect modification of predictors by time since cART initiation (non-proportional hazards) by fitting an interaction between each predictor and time and testing the interaction using the likelihood ratio test. For the purposes of this evaluation we split time at 12 months following start of cART. We based this on the timing of clinical and laboratory evaluations and the plausibility of changing predictors after approximately one year on cART. We initially assessed for association between factors and mortality in univariable analyses. Factors that were associated with mortality with a $p < 0.1$ were included in a multivariable model; we also included age and sex, *a priori*, in the model. Factors no longer showing evidence of an association with mortality in the multivariable model were removed in a step-wise manner. In the multivariable model, we included an interaction with duration on cART for all factors where there was evidence of violation of the proportional hazards assumption. All univariable and multivariable models and mortality rate calculations included clinic site as a random effect, using frailty to control for residual clinic-level confounding and potential clustering at clinic level. For each variable we included a missing value category. We did not model casual pathways (such as between HIV RNA suppression, CD4 count, and death) as our goal was to provide an overall view of predictors of mortality that could enable a clinician at a given time point to assess mortality risk based on available data.

We assessed median CD4 count, by time period, from cART initiation among subjects who survived that time period and subjects who died during that time period. Change over time was assessed with mixed effects linear regression for repeated measures or linear regression for non-repeated measures.

Ethical approval for this study was obtained from the University of KwaZulu-Natal, the University of the Witwatersrand, the London School for Hygiene and Tropical Medicine, and Johns Hopkins University.

Results

Subjects

Out of 16,356 cART initiators, we included 15,060 subjects (92%) contributing 27,873 person years of observation with a median duration of follow-up of 1.8 years (interquartile range [IQR] 0.5-3.0). We excluded 1,296 cART initiators because they lacked identifiers to link with mortality data. Subjects from the community clinics were excluded if they did not have a recorded national identification number. Of the included subjects, 8,102 (54%) were from community-based clinics, 9,605 were men (64%), the median age at cART initiation was 38 years (IQR: 32-45), the median BMI was 22 kg/m² (IQR: 20-26), the median haemoglobin for men was 13.1 g/dL (IQR: 11-14) and for woman was 11.4 (IQR: 9.9-13), the median CD4 count was 127 cells/mm³ (IQR: 58-199), and 9,255 (61%) had a WHO clinical stage III or IV condition (Table 1). Excluded subjects (those without national identification numbers on file), when comparing included and excluded by clinic, were more likely to be men and had a median CD4 count 6 cells/mm³ lower than those who were included.

During observation, 2,658 (18%) subjects died or were medically separated (2,323 patients died, 980 were identified by routine reporting and 1343 from the vital statistics registry, and 339 were medically separated), 628 (4.2%) discontinued cART, 2,282 (15%) transferred out, and 3,522 (23%) were lost to follow-up.

Mortality

Mortality was highest early during cART with a mortality rate of 34 (95% confidence interval [CI] 28-41) per 100 person-years (PYs) for 0 to 3 months; 12 (95% CI 9-14) per 100 PYs for 4-6 months; 6.3 (95% CI 5.1-7.8) for 7-12 months; 3.9 (95% CI 3.2-4.8) for 13-24 months; and 3.3 (95% CI 2.6-4.1) per 100 PYs for 25-48 months (Figure 1).

Associations with mortality

In univariable analysis, factors at cART initiation associated with increased mortality were male sex (hazard ratio [HR] 1.3, $p < 0.001$), age (HR 1.2 per 10 years, $p < 0.001$), BMI < 18.5 kg/m² (HR 2.6, $p < 0.001$), WHO clinical stage III or IV (HR 1.9, $p < 0.001$), haemoglobin < 10 g/dL (HR 2.3, $p < 0.001$), lower CD4 count (p for trend < 0.001), log₁₀ HIV RNA > 4.7 c/mL (HR 1.6, $p < 0.001$), TB-type symptoms (HR 2.1, $p < 0.001$), and not receiving cotrimoxazole (1.2, $p < 0.001$). There was evidence of the proportional hazards assumption being violated for the baseline factors WHO clinical stage, haemoglobin, CD4 count, HIV RNA, and TB symptoms, for which there was an attenuation in hazard of mortality between the early period and later time periods (all non-proportional hazards $p < 0.05$; Table 2).

Univariable analysis of time-updated factors identified BMI < 18.5 kg/m² (3.1, $p < 0.001$), time-updated haemoglobin < 10 g/dL (HR 4.6, $p < 0.001$), lower time-updated CD4 count

($p < 0.001$), lack of HIV RNA suppression after 6 months of cART (HR 9.1, $p < 0.001$), and time updated tuberculosis type symptoms (HR 3.3, $p < 0.001$) as being associated with increased mortality. Among time updated factors, low CD4 count and lack of HIV RNA suppression had an increasing association with mortality over time on cART (p for non-proportional hazards < 0.05 , Table 3).

In the adjusted model we included the following characteristics at cART initiation: sex, age, WHO stage, and cotrimoxazole; time-updated values were used for all other included variables. The final adjusted multivariable model included sex, age, WHO clinical stage at cART initiation, cotrimoxazole use and time updated BMI, CD4 count, TB-type symptoms, haemoglobin, and HIV RNA suppression. Interactions with time were modeled for WHO clinical stage, CD4 count, and HIV RNA suppression (Table 3). No significant changes in association by time were found for the other time updated factors included in the adjusted multivariable model ($p < 0.05$ for interaction with time for BMI, haemoglobin, cotrimoxazole, and TB type symptoms). We completed a sensitivity analysis by excluding medical separations from our death definition and the results were similar with respect to variables in the adjusted model and size of the hazard ratios.

Mortality by time period and median CD4 count, haemoglobin, and BMI

We observed an increase in CD4 count over time on cART in both those who survived and those who eventually died (p for trend < 0.001 ; Table 4). The median CD4 count at cART initiation for patients who survived the first 3 months was 190 cells/mm³ compared to 71 cells/mm³ among those who died during this period ($p < 0.001$). By 37-48 months, the median CD4 count among individuals surviving was 382 cells/mm³ compared to 175 cells/mm³ among subjects who died during that period ($p < 0.001$). Thus, although the median CD4 count among those who died was lower than those who survived for any given time period, between 37- 48 months the median CD4 count among those who died was similar to the CD4 count among survivors during 0-3 months on cART.

Discussion

Our study extends the understanding of changes in mortality risk during cART in a resource limited setting. We have developed a model that estimates the hazard of mortality, based on individual clinical characteristics, from initiation up to 48 months on cART. By using time updated covariates and up to 4 years of follow-up, we have been able to account for longitudinal changes that lead to changes in predicted individual mortality over time.

In our study the mortality rate throughout follow-up was higher than in some prior reports, with previous reports of mortality in the first months of cART of 12.5 – 41 per 100 PYs^{7;22;23;25;26;28-30;36;37}. The finding of high mortality during cART may reflect better ascertainment of deaths through linkage to a vital statistics registry as loss to follow-up without death ascertainment may inflate survival estimates. Other studies that also applied rigorous methods to ascertain deaths reported marked increases in mortality ascertainment ranging between 2.4 and 5.3 fold³⁸⁻⁴¹. By 25 to 48 months on cART, mortality declined considerably to 3.4 deaths per 100 PYs. However, this rate is 3-fold higher than for an age and sex matched general South African population⁴².

Given the lifelong nature of cART it is essential to assess changing predictors of death over time. Factors strongly associated with mortality at cART initiation were CD4 count, haemoglobin, and BMI. This is consistent with findings from several other studies ^{4;7;21-24;28;31;36;40;43-49}. However, the risk of death associated with these characteristics when only the values at cART initiation were used waned over time on cART. This is presumably due to recovery from acute illnesses that may have led to anemia and malnutrition and to a CD4 count rise on cART. The implication is that individuals initially at high risk for mortality do not have persistently increased risk if they survive the first 12 months of cART.

Furthermore, the overall profile of individuals dying after 3 years on cART is different from those dying at cART initiation. For example, by 3-4 years on cART, the median CD4 count among individuals who died was similar to the median CD4 count among survivors during the first 3 months. A possible explanation for this finding is that conditions less associated with the most profound immunosuppression accounted for a larger fraction of deaths over time. If true, this is consistent with changes seen in Europe and North America in which non-AIDS defining illnesses account for an increased proportion of deaths ^{16;50;51}. Further work is needed to accurately determine specific causes of death over-time on cART.

We found that achieving or maintaining HIV RNA suppression was a stronger predictor of survival later on cART than during the first 12 months with an adjusted hazard ratio of 5.6 after 12 months on cART. This finding has important implications for monitoring and for assessing the effect of monitoring strategies. Optimal assessment of such strategies may be most informative by focusing on survival after more than 1 to 2 years of cART.

In addition, TB symptoms and anemia predicted death through-out the duration of cART, despite deaths occurring at higher CD4 count. It is likely that multiple illnesses contribute to these signs and symptoms including TB, bacterial and fungal respiratory illnesses, disseminated systemic bacterial infections, viral illnesses, and malignancies. However, it is useful to consider that these symptoms were reported by ambulatory patients attending outpatient clinics, usually for routine follow-up care. Thus symptoms in ambulatory patients should not be ignored as patients in our cohort who had these symptoms progressed to death at an increased rate. An appropriate sign and symptom guided investigation, empiric treatment, and close follow-up of these individuals may have helped to reduce mortality.

Strengths of our study include the large routine HIV care cohort, long observation time, and robust ascertainment of mortality. However, it is important to note several limitations. One limitation is missing data. By using time updated data we are using information from as close to death as possible, but data may be missing because of critical illness, leading to a non-random distribution of missing information. This is especially true as missed clinic visits may both predict and be a result of severe illness. We also lacked adherence data. Failure to maintain virologic suppression suggests inadequate adherence, however, specific behavioral markers may have added further depth to the findings. Finally, we do not have data on cause of death. Knowing this would greatly add to understanding mortality during long term cART.

Our findings re-emphasize the dramatic effect cART has on survival in an HIV treatment program. We observed a 12-fold reduction in mortality between the first 3 months on cART and more than 2-4 years of cART. Furthermore, our findings suggest a possible shift in causes of death during cART. Further work, including accurate identification of the cause of death is needed to confirm these potential changes. This information will be crucial to develop suitable interventions to reduce mortality. Importantly, clinical disease represented by anemia, low BMI, and TB symptoms remain important factors associated with mortality. These findings point to a potential means of reducing mortality with the application of aggressive adherence management, follow-up, prophylactic therapies, routine assessment of BMI and haemoglobin, and empiric therapies for individuals with signs of illness.

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Figure 1. Smoothed instantaneous hazard estimate of death from time of cART initiation (grey shading, 95% confidence interval)

Table 1

Cohort characteristics at cART initiation (N=15,060)

	N (%)
Sex	
Female	5,455 (36)
Male	9,605 (64)
Missing	0
Age (years)	
30	2,687 (18)
31-35	2,962 (20)
36-40	3,056 (20)
41-45	2,644 (18)
46	3,711 (24)
Missing	0
BMI group	
<18.5	898 (6)
18.5-24	3,416 (23)
25	2,039 (14)
Missing	8,707 (58)
WHO clinical stage	
1 & 2	5,521 (37)
3 & 4	9,255 (61)
Missing	284 (2)
Haemoglobin (g/dl)	
<10	1,681 (11)
10	8,908 (59)
Missing	4,471 (30)
CD4 (cells/mm ³)	
Median	127 (58-199)
50	3,112 (21)
51-100	2,527 (17)
101-200	4,894 (32)
201-350	2,725 (18)
>350	699 (5)
Missing	1,103 (7)

	N (%)	
HIV RNA (log ₁₀ c/mL)	Median	4.7 (4.6-5.0)
TB symptoms*	No	6,281 (42)
	Yes	5,714 (38)
	Missing	3,065 (20)
Cotrimoxazole at cART start	No	6,960 (46)
	Yes	8,110 (54)
NRTI used	AZT+3TC	7,038 (47)
	D4T+3TC	7,449 (49)
	Other	573 (4)
NNRTI or PI used	EFV	10,736 (71)
	NVP	3,620 (24)
	Other	704 (5)

* TB symptoms: any self-reported cough, sputum production, fever, night sweats, or weight loss

Table 2
Change in strength of association with mortality over time for characteristics at cART initiation, univariable analysis

Value at cART initiation	<12m HR*	12m HR*	P for non-proportional hazards for <12m & 12m
Sex			
Female	Referent	Referent	0.2
Male	1.3 (1.2-1.5)	1.2 (0.99-1.4)	
Age (years)			
30	Referent	Referent	0.3
31-35	1.1 (0.97-1.3)	0.95 (0.71-1.3)	
36-40	1.3 (1.1-1.5)	0.82 (0.61-1.1)	
41-45	1.4 (1.2-1.6)	1.0 (0.78-1.4)	
46	1.5 (1.3-1.8)	1.2 (0.89-1.5)	
BMI (kg/m²)			
<18.5	2.8 (2.3-3.3)	2.2 (1.6-3.2)	0.1
18.5-24	Referent	Referent	
25	0.65 (0.53-0.80)	0.80 (0.59-1.1)	
WHO stage			
1 & 2	Referent	Referent	0.0001
3 & 4	2.2 (2.0-2.4)	1.2 (1.0-1.4)	
Haemoglobin (mg/dL)			
<10	2.7 (2.4-3.0)	1.3 (1.0-1.7)	0.0001
10	Referent	Referent	
CD4 (cells/mm3)			
50	5.5 (4.0-7.7)	2.3 (1.4-3.8)	<0.0001
51-100	3.1 (2.2-4.3)	1.9 (1.1-3.2)	
101-200	1.8 (1.3-2.5)	1.5 (0.90-2.4)	
201-350	1.2 (0.82-1.6)	1.1 (0.65-1.9)	
>350	Referent	Referent	
Log10 HIV RNA (c/mL)			
4.70 (50,000)	Referent	Referent	0.0001
>4.70 (50,000)	1.7 (1.6-1.9)	1.2 (1.0-1.4)	
TB symptoms			
No	Referent	Referent	<0.0001
Yes	2.3 (2.1-2.6)	1.4 (1.1-1.7)	
No visit	1.4 (1.2-1.6)	0.61 (0.44-0.84)	
Cotrimoxazole			
No/unknown	Referent	Referent	0.1

Value at cART initiation	<12m HR [*]	12m HR [*]	P for non-proportional hazards for <12m & 12m
Yes	0.77 (0.70-0.84)	0.89 (0.75-1.0)	

* controlling for clinic-level effects using frailty random effects

** TB symptoms: any self-reported cough, sputum production, fever, night sweats, or weight loss

Table 3

Univariable and multivariable associations with mortality. Factors with a change in association by time from cART initiation are presented with hazard ratios during the period of <12m on cART and 12 on cART (n=15,060)

	Deaths / person years	Univariable Hazard ratio*	P	Adjusted hazard ratio* (95% CI)	P
Sex					
Female	952/10,545	Referent	<0.001	Referent	0.004
Male	1706/17,327	1.3 (1.2-1.4)		1.2 (1.0-1.3)	
Age (per 5 year increase)					
		1.1 (1.1-1.1)	<0.001	1.1 (1.1-1.1)	<0.001
BMI (kg/m²), time updated					
<18.5	394/1230	3.1 (2.7-3.5)		1.9 (1.7-2.2)	
18.5-24	635/8106	Referent	<0.001	Referent	<0.001
25	296/7181	0.64 (1.6-2.0)		0.84 (0.73-0.97)	
Missing	1333/11,354	1.8 (1.6-2.0)		1.3 (1.2-1.5)	
WHO stage at cART initiation					
0-<12 months cARTⁱ					
1 & 2	474/4647	Referent	<0.001	Referent	<0.001
3 & 4	1517/7094	2.2 (2.0-2.4)		1.6 (1.4-1.7)	
12 months cARTⁱ					
1 & 2	214/6174	Referent	0.02	Referent	0.2
3 & 4	361/8894	1.2 (1.0-1.4)		1.1 (0.93-1.3)	
TB symptoms^{**}, time updated					
No	466/15,683	Referent	<0.001	Referent	<0.001
Yes	541/2957	3.3 (2.9-3.8)		2.4 (2.1-2.7)	
No visit	1666/9234	5.7 (5.1-6.3)		4.5 (4.0-5.0)	
Haemoglobin (g/dL), time updated					
<10	765/1533	4.6 (4.2-5.1)		2.6 (2.3-2.8)	
10	1546/24,687	Referent	<0.001	Referent	<0.001
CD4 count (cells/mm³), time updated					

	Deaths / person years	Univariable Hazard ratio*	P	Adjusted hazard ratio* (95% CI)	P
0- <12 months cARTⁱⁱ					
50	741/804	13 (19-34)		5.2 (4.2-6.4)	
51-100	367/1128	5.2 (4.3-6.6)		2.8 (2.2-3.4)	
101-200	455/3254	2.4 (2.0-3.0)		1.7 (1.4-2.1)	
201-350	268/3839	1.3 (1.0-1.6)		1.2 (0.94-1.5)	
>350	113/2305	Referent	<0.001	Referent	<0.001
12 months cARTⁱⁱ					
50	112/391	25 (19-34)		6.7 (4.9-9.2)	
51-100	95/637	13 (9-17)		4.5 (3.3-6.2)	
101-200	148/2509	5.0 (3.8-6.5)		2.5 (1.9-3.3)	
201-350	139/4961	2.3 (1.8-3.1)		1.6 (1.2-2.2)	
>350	78/6508	Referent	<0.001	Referent	<0.001
HIV RNA log₁₀ at cART initiation					
<4.7	1291/16,806	Referent	<0.001		
4.7	1367/11,066	1.6 (1.4-1.7)			
HIV RNA suppression on cART (>6m after cART start), time updated					
0- <12 months cARTⁱⁱⁱ					
400 c/mL	180/782	5.8 (4.5-7.2)		2.6 (2.0-3.2)	
<400 c/mL	121/2492	Referent	<0.001	Referent	<0.001
12 months cARTⁱⁱⁱ					
400 c/mL	443/2826	13 (10-16)		5.6 (4.4-7.0)	
<400 c/mL	100/6986	Referent	<0.001	Referent	<0.001
Cotrimoxazole					
No/unknown	1158/10,843	Referent	<0.001	Referent	<0.001
Yes	1515/17,031	0.79 (0.73-0.87)		0.82 (0.75-0.89)	

* controlling for clinic-level effects using frailty random effects

** TB symptoms: any self-reported cough, sputum production, fever, night sweats, or weight loss

ⁱ p for interaction between WHO stage and time in adjusted analysis (<12m, 12m, 0.0006

ii p for interaction between time updated CD4 and time in adjusted analysis (<12m, 12m), 0.002

iii p for interaction between virologic suppression and time in adjusted analysis (<12m, 12m), <0.0001

Table 4

Median CD4 by time from cART initiation

	0-3 months	4-6 months	7-12 months	13-24 months	25-36 months	37-48 months
n	13,762	12,915	9,988	7,932	5,896	3,110
CD4 (cells/mm³), median (IQR)						
Died*	71 (24-154)	72 (26-158)	130 (57-219)	148 (65-255)	154 (63-297)	175 (90-268)
Alive**	190 (111-289)	205 (124-311)	246 (161-353)	297 (197-420)	351 (232-490)	382 (249-543)

* P for trend, linear regression, <0.001

** P for trend, random effects, <0.001