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Incidence rate of and factors associated with loss-to-follow-up in a longitudinal cohort of anti-retroviral treated HIV-infected persons: an AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) analysis

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Abstract

Purpose—Examine incidence and factors associated with loss to follow-up (LTFU) in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort.

Method—ALLRT is a prospective cohort of HIV-infected persons randomized to ARV regimens/strategies in ACTG trials and followed long-term after the trial ends. Person-years were calculated from ALLRT entry until LTFU (defined using off-study reasons or ≥ 3 consecutive missed visits), death/severe debilitation/site closures, or June 2009 (censored). Poisson regression was used to examine LTFU factors separately among participants who were ARV-naïve or ARV-experienced at trial entry.

Results—Among 4630 participants (22,524 person-years), 1140 were lost to follow-up, 237 died, 29 were severely debilitated, and 443 were at sites that closed. The LTFU incidence was 5.5 and 4.2 per 100 person-years among previously ARV-naïve and ARV-experienced participants, respectively. In both groups, age ≤ 50 , site location, being off-ARVs and viral load ≥ 400 copies/ml were associated with a higher risk of LTFU. Among ARV-naïves, male sex, education < 16 years, IV drug use and cigarette smoking were also associated with LTFU.

Conclusion—Knowledge of differential LTFU can help researchers identify participants at risk of LTFU in longitudinal HIV cohorts and design retention strategies, thereby limiting study bias. The identified factors should be included in inverse probability of weighting models to account for LTFU.

Keywords

Loss to follow-up; HIV; prospective cohort; bias; risk factors; incidence

Introduction

Prospective cohort studies provide valuable information about long-term effects of antiretroviral (ARV) therapy regimens, as well as AIDS related and non-AIDS related clinical outcomes among HIV-infected persons. Studies that extend over long durations, however, may be subject to losses to follow-up.

Knowledge of factors related to loss to follow-up (LTFU) can help to characterize the study population and to devise methods to improve retention rates in HIV cohort studies (1). For a particular analysis, if participants are lost for reasons related to the exposure of interest, the analytic outcome or both, the results may be biased. Recent findings suggest that LTFU leads to an overestimation of survival rates in HIV-infected persons in developed countries (2) and creates substantial bias in studies performed in resource-limited settings (3). Statistical methods such as inverse probability of censoring weighting (IPCW) can be used to address informative censoring due to selective follow-up (4). Even if LTFU is non-differential, generalizability of study results may be affected. A comparison of those who remain on study with those who are lost to follow-up can help guide the analysis of data and interpretation of study results. Loss of participants over time also lowers the statistical power of a study as persons with missing data are often excluded from analyses. Additionally, retaining HIV-infected patients in care, even in the context of continued clinical trial participation, can help improve disease management, since low retention rates are associated with adverse outcomes and lower survival (5).

The purpose of this analysis is to identify factors related to LTFU in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort. The ALLRT cohort is made up of participants who were randomized to specific ARV regimens in ACTG clinical trials, and followed long-term after the end of the parent clinical trial. Participants were either ARV-naïve or ARV-experienced when they entered their parent trial, and these groups differed with respect both to prior ARV treatment as well as prior ACTG study experience; so we examined LTFU separately in both groups.

Methods

ALLRT is a prospective cohort of HIV-infected participants (age ≥ 13 years) who were randomized to receive ARV therapy regimens, immune-based therapies or treatment strategies in selected ACTG clinical trials (6). Of the 26 ACTG trials that are parent clinical trials for ALLRT, six parent trials enrolled participants who were ARV-naïve at entry, 18 enrolled participants who were ARV-experienced at entry and two enrolled both. ACTG sites that enrolled participants to ALLRT received approval by their designated institutional review boards to conduct this study, and all ALLRT participants provided written informed consent. Enrollment in ALLRT began in 2000 and is ongoing.

Follow-up begins when a participant enrolls in his/her ACTG parent trial; participants enroll in ALLRT within 16 weeks of starting on their parent trial (prior to 2006, participants could enroll in ALLRT anytime during or 8 weeks after the end of the parent trial); follow-up of participants continues in ALLRT after the parent trial ends. ALLRT visits are scheduled every 16 weeks. Data are recorded by the study site staff using standard ACTG case report forms. Demographic data on age, race/ethnicity, sex and years of education are collected either at parent trial entry or at ALLRT entry. Behavioral characteristics including cigarette smoking history and IV drug use history are also collected at parent trial entry or ALLRT entry, and smoking status is updated during follow-up in ALLRT. Clinical data including medical diagnoses (AIDS-defining and non-AIDS defining), ARV medications, HIV-1 RNA and CD4+ T-cell counts are obtained at entry and during follow-up. Mortality data are

obtained from death certificates, hospital or outpatient records and other source documentation.

Definition of LTFU

As defined by the ALLRT protocol, a participant who misses three or more consecutive ALLRT protocol visits (no ALLRT protocol visits for 48 consecutive weeks or more) and cannot be found for the purposes of obtaining information related to survival and/or occurrence of confirmed clinical end-points is considered lost to follow-up. Site personnel complete an “off-study” form for all such persons; the form includes an off-study date and reasons for study discontinuation, and is filled out at or after the third missed visit. For this analysis, the following off-study reasons were used to define LTFU: 1) subject unable to get to clinic (n=394), 2) subject withdrew consent (n=193), 3) subject not willing to adhere to study requirements (n=110), and 4) site unable to contact subject (n=380). Using the off-study form, 1,077 participants in the ALLRT cohort were reported as lost.

In addition, participants in the ALLRT cohort who missed three or more consecutive protocol visits, and did not have a completed off-study form in the database were considered lost if site personnel reported no contact with the participant for three consecutive scheduled visits (N= 63) on the study visit form. Based on these definitions, 1140 participants in total were considered as lost to follow-up; the date of LTFU was defined as 16 weeks following the last clinic visit. Known deaths, severe debilitations (precluding in-person visits but with phone or clinic contact) and participants whose follow-up was terminated because of site closure were not considered LTFU (N=709); site closure was considered a form of administrative censoring since participants ended follow-up regardless of their demographics and clinical characteristics.

Analysis

Since the focus of this analysis was on LTFU within ALLRT, person-years were calculated from ALLRT enrollment to LTFU; death, severe debilitation, site closure; or end of follow-up (June 2009). In addition to the 1140 participants classified as LTFU based on our case definition, 115 participants missed three consecutive visits during follow-up but then returned to regular clinic visits. For the main analysis, these participants were considered to have remained on-study; in a sensitivity analysis, these participants were reclassified as lost to follow-up when three visits were missed.

Incidence rate of LTFU was calculated as the number LTFU divided by total person-years of follow-up. Poisson regression was used to examine associations between demographic, behavioral and clinical factors and LTFU.

Demographic factors examined included age (in years) at ALLRT enrollment, sex, race/ethnicity, and years of education. Behavioral factors included history of IV drug use at enrollment, and history of smoking. Clinical characteristics included CD4+ T-cell count, HIV-1 RNA, ARV therapy status, body mass index (BMI, kg/m²), and diagnosis of AIDS-defining events, diabetes, myocardial infarction and stroke. The location of the site that enrolled the participant into ALLRT was used to classify participants into four geographic regions: Northeast, Midwest, South and West.

CD4+ T-cell count, HIV-1 RNA, ARV therapy status, BMI and smoking history were included as time-updated covariates. Each participant's follow-up time from enrollment was divided into 16-week intervals. We examined the association between BMI, HIV-1 RNA, ARV treatment status (off ARVs for entire 16-week period versus any ARV use) and CD4+ T-cell count for a 16-week interval, and risk of LTFU in the next interval. Smoking history was updated for every 16-week interval as 1) yes, if participants reported a prior history of

smoking, and 2) no, if the subject had no prior smoking history. For each 16-week interval, the number of years since the end of the parent trial was calculated. For missing time-updated covariates, the last-value-carried-forward method was used.

In 2006, participants were required to enroll into ALLRT within 16 weeks of enrolling into their parent clinical trial. Previously, participants could enroll into ALLRT during their parent trial or within 8 weeks after it ended. We evaluated the effect of early versus late ALLRT enrollment on LTFU among participants who enrolled before 2006 (N= 3,413). Early enrollment was defined as enrollment in ALLRT anytime until the end of the parent trial, and late enrollment as enrollment in ALLRT after the end of the parent trial.

A large proportion of the participants who were ARV-experienced when they entered the parent trial had been enrolled in previous ACTG clinical trials. For these participants, we calculated the number of person-years of prior experience within the ACTG and evaluated the association between this measure and LTFU.

Univariate models were used to assess the unadjusted relative risks between variables and LTFU. Variables that were significant ($p < 0.05$) at a univariate level were added to the multivariable model. For the final multivariable model, demographic factors (age, sex, race and education) were included regardless of p-value. For all other variables, only those that were statistically significant ($p < 0.05$) were retained in the final multivariable model. If any level of a multi-level categorical variable (for example, site location) was significant ($p < 0.05$), all levels were retained in the multivariable model. Analyses were performed separately for those participants who were ARV-naïve at parent trial entry and for those who were ARV-experienced at parent trial entry. The multivariate model was first developed for the ARV-naïve group; for comparison, the same multivariate model was used for the ARV-experienced group. All analyses were performed using SAS version 9.0 (SAS Institute Inc, Cary, NC).

Results

There were 4,630 participants who enrolled in ALLRT between January 2000 and June 2009. Of these, 3,405 were ARV-naïve and 1,225 were ARV-experienced when they entered their parent study. Among 4,630 participants (22,524 person-years), 1,140 were lost to follow-up, 237 died, 29 were severely debilitated, and 443 were enrolled at sites that closed. The overall rate of LTFU was 5.1 per 100 person-years.

Participants who were ARV-naïve at parent trial entry

Among 3,405 participants (15,210 person-years) who were ARV-naïve when they enrolled in their parent trial, 834 were LTFU, 120 died, 16 were severely debilitated, and 322 were followed at sites that closed. The overall rate of LTFU in this group was 5.5 per 100 person-years. Demographic and clinical characteristics at ALLRT enrollment are shown in table 1. Younger participants, males, smokers and intravenous (IV) drug users were more likely to be in the LTFU group (table 1).

Consistent with univariate analyses, the final multivariate model (table 2) indicated that male sex, younger age, education < 16 years, IV drug use, time-updated smoking, shorter time since end of parent study, site location and time-updated HIV-1 RNA ≥ 400 copies/ml were independently associated with LTFU. As expected, time-updated HIV-1 RNA viral load and ARV status were highly correlated (86% of the 16-week time intervals with an off-ARV status also had a HIV-1 RNA ≥ 400 , and 89% of the 16-week time intervals with an on-ARV status had a HIV-1 RNA < 400), and were not included together in the models. In a multivariate model that included demographics, IV drug use, smoking history and site

location (but did not include HIV-1 RNA), being off ARVs was positively associated with LTFU (RR=3.41, 95% confidence interval (CI) =2.82, 4.13). Similar results were obtained when we examined LTFU factors separately for the two most common off-study reasons: subject unable to get to clinic, and site unable to contact subject (details not shown).

We also assessed the influence of pre-ARV treatment HIV-1 RNA (median log₁₀ HIV-1 RNA=4.7) and CD4 T-cell count (median =217 cells/mm³). Neither factor was associated with LTFU when added to the multivariate model (RR (95%CI) for pre-ARV CD4: 0.98(0.82, 1.17) for CD4≤200 and 0.97 (0.81, 1.17) for CD4 201-350 versus CD4>350 cells/mm³; RR (95%CI) for HIV-1 RNA>10,000= 1.11(0.88, 1.41) versus <10,000 copies/ml, p>0.5).

A decline in the LTFU rate over time was seen as the number of years of follow-up increased (univariate relative risk (RR) = 0.66, ≥6 years versus 0-2 years, p-value<0.001). There were 2,188 ARV-naïve participants who enrolled in ALLRT before 2006; in a multivariate model that included demographics, IV drug use, smoking history, site location, years since end of parent study and HIV-1 RNA, the RR for early versus late enrollment was 0.58 (95% CI=0.41, 0.82, p-value=0.002) (model not shown). Finally, 83 participants had missed three consecutive visits during follow-up, but then returned to regular study visits and were classified as being on-study for the main analysis; analyses were repeated after reclassifying these participants as LTFU, and similar results were obtained (model not shown).

Participants who were ARV-experienced at parent trial entry

Among 1225 participants (7,314 person-years) who were ARV-experienced at parent trial entry, 306 were LTFU, 117 died, 13 were severely debilitated, and 121 were at sites that closed. The overall rate of LTFU was 4.2 per 100 person-years. Demographic and clinical characteristics at ALLRT enrollment are shown in table 1.

The multivariable model is presented in table 3. Similar to the model for the ARV-naïve group, younger age and HIV-1 RNA ≥400 copies/ml were associated with LTFU. Time-updated ARV status was evaluated in a separate model, without HIV-1 RNA, and off-ARV status was similarly associated with LTFU. Similar findings were obtained when we examined LTFU factors separately for the two most common off-study reasons: subject unable to get to clinic, and site unable to contact subject (details not shown).

Similar to the ARV-naïve group, the LTFU rate declined as the number of follow-up years increased (univariate RR=0.71, ≥6 years versus 0-2 years, p-value=0.04). More than half of the ARV-experienced participants had been enrolled in ACTG trials before they enrolled in their ALLRT parent trial; mean number of years of prior research study experience within the ACTG was 2.2 years (median=4 weeks, maximum= 17.4 years). When added in the multivariable model described in table 3, the RR for each year increase in the number of years of ACTG experience prior to parent trial entry was 0.9 (95% CI= 0.86, 0.95, p-value<0.001).

Thirty-two participants had missed three consecutive visits during follow-up but then returned to regular clinic visits, and were classified as being on-study. When these participants were classified as LTFU, similar results were obtained.

Discussion

We investigated LTFU in 4,630 HIV-infected patients enrolled in a unique long-term cohort study of randomized clinical trial participants (6). The overall rate of LTFU was 5.1 per 100

person-years, minimally higher than the rates observed in the French clinical HIV cohorts and EuroSIDA (4.3, 3.5 and 3.7 per 100 person-years) (7-9); in US-based cohorts, LTFU was 3.0% and 3.9% per year in the MACS and the WIHS, respectively (10, 11). In contrast to clinical cohorts, evaluations in the ALLRT research protocol may or may not be linked to their clinical care. The relatively low rate of LTFU reflects the commitment of ALLRT volunteers and ACTG sites to the study of long-term outcomes which are increasingly relevant in the context of life-long anti-HIV therapy (12).

A key finding was that the rate of LTFU declined as the duration of participation in the study increased. LTFU was also slightly lower in the ARV-experienced group when compared to the ARV-naïve group likely due to familiarity of the ARV-experienced participants with treatment for HIV and the importance of follow-up, as well as experience with the sites and ACTG clinical trials. The risk of LTFU decreased by 8% for every additional year participants had been involved with the ACTG when they entered their ALLRT parent trial. To our knowledge, our study is the first to report on factors associated with LTFU separately among participants who were ARV-naïve and starting their first ARV regimen, and those who were ARV-experienced at parent trial entry. Factors related to LTFU were similar for both groups of participants.

Participants who were off ARV medications were more likely to be lost to follow-up. Not surprisingly, participants who were off ARVs for extended periods had poorly controlled viremia; most HIV-1 viral loads were ≥ 400 when participants were off-ARVs for the entire 16-week time interval; and most HIV-1 viral loads were < 400 when participants were not off-ARVs for the entire 16 weeks interval. Poorly suppressed HIV-1 viral load was also an independent risk factor for LTFU; similar findings have been reported by other cohorts (10, 13). Pre-ARV treatment HIV-1 RNA was not associated with LTFU. Lack of viral suppression could be indicative of poor adherence to ARV therapy, complex health issues or psychosocial stresses. Recent evidence suggests that social factors such as income, poor living conditions and lack of social support and stability are associated with poor adherence to treatment in HIV patients (14); these social factors could also affect the ability of patients to adhere to regular clinic visits.

Our results also show that younger participants and males were more likely to be lost to follow-up; similar observations have been reported in previous studies (11, 13, 15-18). Younger participants may be more difficult to retain in long-term follow-up because they are geographically more mobile. Census data show that over one-third of all people who moved location in the US between 1995 and 2000 were between 25-39 years of age (19), and this pattern could have continued beyond 2000. It is also possible that younger participants have lifestyle factors such as work or school that prevent them from adhering to regular study visits.

The risk of being lost to follow-up increased among participants who had fewer years of education. Persons with less education may have employment-related issues such as not having enough time off from work to attend clinic visits (20, 21). Educated participants may be more motivated to maintain study participation because of their ability to understand study benefits such as laboratory results and new scientific information about HIV and its treatment (10).

Behavioral characteristics, such as IV drug use and cigarette smoking, may reflect a lifestyle that makes it harder to adhere to treatment regimens and scheduled study visits. Consistent with other studies, our results show that the risk of LTFU was higher among those with a history of IV drug use (7, 18, 22, 23), and among smokers (10).

We found regional differences in LTFU; participants from sites in the Northeast had a lower risk of LTFU relative to those from the South. Reports from the U.S. Census state that the South had the highest rate of migration between 1995 and 2000, and between 2000 and 2004, while the Northeast had the lowest (24, 25), consistent with the regional differences in LTFU. These high rates of migration could have resulted in participants missing study visits and being considered lost to follow-up.

Our study has limitations. The ALLRT database is not yet linked to national death index databases; some participants who were classified as LTFU may have died, which could have overestimated the LTFU rate. In addition, ALLRT did not collect information on health insurance, incarceration, alcohol use and specific illicit drug use (for example, heroin or cocaine use), and these are variables that have been linked to LTFU in other analyses [7, 11, 26]. Considering the life-long nature of HIV therapy, we were not able to assess whether participants lost from follow-up from the ALLRT research protocol remained in clinical care apart from their research participation (27-29).

To retain participants in follow-up, the ACTG has standard procedures for facilitating the transfer of participants between sites. At individual sites, a variety of retention strategies are employed such as reimbursement for time and transportation, provision of child care, refreshments or other reimbursements such as grocery vouchers; all are approved by local institutional review board guidelines. ALLRT has been able to maintain most of the enrolled participants in long-term follow-up, with a median follow-up of 6 years for the ARV-experienced participants and 4.5 years for the participants who were ARV-naïve at entry. The factors associated with LTFU in ALLRT are similar to those reported by other HIV cohorts. Our results indicate that specific subgroups of participants including those who may be at greater risk for clinical progression are at a higher risk of being lost to follow-up; special efforts should be made to retain such participants in follow-up. Knowledge of factors associated with LTFU is important to correctly construct the weights used in analytic methods like IPCW that address informative censoring and bias due to selective follow-up (4, 30,31). Our findings suggest that antiretroviral therapy status, virologic suppression status, age, sex and education should be included in future analyses addressing informative censoring. The findings from this study can help clinicians and researchers identify participants at high risk of LTFU in longitudinal HIV cohorts and design strategies to improve retention, thereby limiting study bias, and providing the long-term data needed to assess HIV outcomes.

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Table 1

Characteristics at ALLRT enrollment.

Characteristic		ARV-naïve at parent entry (N=3,405)		ARV-experienced at parent entry (N=1,225)	
		Lost to follow-up (N=834)	On-study (N=2,571)	Lost to follow-up (N=306)	On-study (N=919)
Sex	Male	715 (86)	2,076 (81)	275 (90)	795 (87)
	Female	119 (14)	495 (19)	31 (10)	124 (13)
Race/Ethnicity	Black Non-Hispanic	264 (32)	817 (32)	67 (22)	181 (20)
	Hispanic/Other	195 (23)	638 (25)	79 (26)	172 (19)
	White non-Hispanic	375 (45)	1,116 (43)	160 (52)	566 (62)
Age (years)	≤30	178 (21)	430 (17)	24 (8)	28 (3)
	31-40	410 (49)	935 (36)	115 (38)	244 (27)
	41-50	195 (23)	840 (33)	130 (42)	417 (45)
	>50	51 (6)	366 (14)	37 (12)	230 (25)
Education (years)	0-12	324 (39)	1000 (39)	86 (28)	291 (32)
	13-15	331 (39)	888 (35)	122 (40)	273 (30)
	≥16	178 (22)	682 (26)	98 (32)	355 (39)
	Missing	1	1	-	-
Smoking history	Yes	543 (65)	1,400 (54)	193 (63)	549 (60)
	No	284 (34)	1,127 (44)	109 (36)	364 (40)
	Missing	7 (1)	44 (2)	4 (1)	6 (1)
IV drug use history	Current/previous	92 (11)	216 (8)	39 (13)	99 (11)
	Never	742 (89)	2,355 (92)	267 (87)	820 (89)
Body mass index (kg/m ²)	≥30	129 (15)	446 (17)	38 (12)	95 (10)
	25-29	272 (33)	909 (35)	107 (35)	314 (34)
	<25	429 (51)	1211 (47)	155 (51)	505 (55)
	Missing	4	5	6 (2)	5 (1)
CD4+ T-cell count (cells/mm ³)	Median (Q1-Q3)	340 (197, 523)	328 (193, 480)	419 (283, 611)	408 (248, 601)
HIV-1 RNA viral load (copy/ml)	Median (Q1-Q3)	96 (49, 29,648)	49 (49, 14,133)	66.5 (49, 6,528)	49 (49, 5,288)
History of AIDS-defining illness	Yes	150 (18)	494 (19)	87 (28)	258 (28)

Characteristic		ARV-naïve at parent entry (N=3,405)		ARV-experienced at parent entry (N=1,225)	
		Lost to follow-up (N=834)	On-study (N=2,571)	Lost to follow-up (N=306)	On-study (N=919)
History of diabetes	No	684 (82)	2,077 (81)	219 (72)	661 (72)
	Yes	19 (2)	111 (4)	29 (9)	70 (8)
	No	815 (98)	2,460 (96)	277 (91)	849 (92)
History of MI	Yes	6 (1)	27 (1)	3 (1)	22 (2)
	No	828 (99)	2,544 (99)	303 (99)	897 (98)
History of stroke	Yes	6 (1)	22 (1)	3 (1)	19 (2)
	No	828 (99)	2,549 (99)	303 (99)	900 (98)
Geographic location of the site	North-east	122 (15)	506 (20)	49 (16)	226 (25)
	West	193 (23)	590 (23)	72 (24)	174 (19)
	Mid-West	226 (27)	736 (29)	88 (29)	282 (31)
	South	293 (35)	739 (29)	97 (32)	237 (26)

Values are N(%) unless otherwise stated.

Table 2

Univariate and multivariate analyses for participants who were ARV-naïve at parent study entry.

	Person-years	Univariate		Multivariate	
		RR (95% CI)**	p-value	RR (95% CI)**	p-value
Sex					
Male	12358	1.39 [1.14, 1.68]	<0.001	1.34 [1.09, 1.63]	0.005
Female	2852	1.0		1.0	
Race/Ethnicity					
Black Non-Hispanic	4746	1.01 [0.86, 1.18]	>0.9	0.93 [0.79, 1.10]	0.40
Hispanic/Other	3660	0.97 [0.81, 1.15]	0.70	0.87 [0.72, 1.05]	0.15
White Non-Hispanic	6804	1.0		1.0	
Age (years) at ALLRT enrollment					
≤30	2444	2.74 [2.00, 3.74]	<0.001	2.48 [1.81, 3.38]	<0.001
31-40	6095	2.53 [1.89, 3.39]	<0.001	2.37 [1.77, 3.17]	<0.001
41-50	4752	1.54 [1.13, 2.10]	0.006	1.44 [1.06, 1.95]	0.02
>50	1918	1.0		1.0	
Education (years)					
0-12	5681	1.35 [1.12, 1.61]	0.001	1.24 [1.03, 1.50]	0.03
13-15	5156	1.45 [1.21, 1.73]	<0.001	1.28 [1.07, 1.54]	0.007
≥16	4371	1.0		1.0	
IV drug use history at ALLRT enrollment					
Yes	1241	1.40 [1.11, 1.75]	0.004	1.26 [1.00, 1.59]	0.05
No	13969	1.0		1.0	
History of AIDS defining illness at ALLRT enrollment					
Yes	2875	0.94 [0.79, 1.12]	0.50	-	-
No	12335	1.0		-	
History of diabetes at ALLRT enrollment					
Yes	584	0.58 [0.37, 0.92]	0.02	-	-
No	14626	1.0		-	

	Person -years	Univariate		Multivariate	
		RR (95% CI) **	p-value	RR (95% CI) **	p-value
History of MI at ALLRT enrollment					
Yes	158	0.69 [0.31, 1.56]	0.37	-	-
No	15052	1.0		-	
History of stroke at ALLRT enrollment					
Yes	121	0.90 [0.41, 1.97]	0.80	-	-
No	15089	1.0		-	
Geographic location of the site					
North-east	2980	0.63 [0.51, 0.78]	<0.001	0.64 [0.52, 0.79]	<0.001
West	3355	0.88 [0.73, 1.06]	0.18	0.90 [0.74, 1.09]	0.28
Mid-West	4385	0.79 [0.66, 0.94]	0.008	0.79 [0.66, 0.94]	0.009
South	4489	1.0		1.0	
Time-updated smoking history					
Yes	8913	1.48 [1.28, 1.71]	<0.001	1.41 [1.22, 1.64]	<0.001
No	6297	1.0		1.0	
Time-updated body mass index (kg/m ²)					
≥30	3083	0.73 [0.60, 0.88]	0.001	-	-
25-29	5684	0.79 [0.68, 0.92]	0.003	-	
<25	6443	1.0			
Time-updated CD4+ T-cell count (cells/mm ³)					
≤350	4426	1.38 [1.20, 1.59]	<0.001	-	-
>350	10784	1.0		-	
Time-updated HIV-1 RNA viral load (copy/ml)					
≥400	2275	2.89 [2.50, 3.34]	<0.001	2.71 [2.34, 3.13]	<0.001
<400	12935	1.0		1.0	
Time-updated ARV status *					
Off ARVs	920	3.33 [2.75, 4.02]	<0.001	-	-
On ARVs	14290	1.0		-	
Years since end of parent study					

	Person -years	Univariate		Multivariate	
		RR (95% CI) **	p-value	RR (95% CI) **	p-value
Every 1 year increase		0.93 [0.89, 0.96]	<0.001	0.92 [0.89, 0.96]	<0.001

* By replacing time-updated viral load with time-updated ARV status in the final multivariate model, we obtain an adjusted RR (95%CI): 3.41 [2.82, 4.13], with p-value <0.001

** RR (95%CI)= Relative risk (95% percent confidence interval)

Table 3

Univariate and multivariate analyses for participants who were ARV-experienced at parent study entry.

	Person years	Univariate		Multivariate	
		RR (95% CI) **	p-value	RR (95% CI) **	p-value
Sex					
Male	6363	1.33 [0.91, 1.94]	0.14	1.39 [0.95, 2.03]	0.09
Female	951	1.0		1.0	
Race/Ethnicity					
Black Non-Hispanic	1383	1.35 [1.01, 1.80]	0.04	1.23 [0.90, 1.67]	0.20
Hispanic/Other	1474	1.49 [1.14, 1.96]	0.004	1.23 [0.91, 1.65]	0.17
White Non-Hispanic	4457	1.0		1.0	
Age (years) at ALLRT enrollment					
≤30	293	3.52 [2.13, 5.83]	<0.001	2.95 [1.79, 4.86]	<0.001
31-40	2179	2.27 [1.56, 3.30]	<0.001	2.06 [1.42, 3.01]	<0.001
41-50	3248	1.72 [1.20, 2.48]	0.003	1.63 [1.14, 2.34]	0.008
>50	1594	1.0		1.0	
Education (years)					
0-12	2156	1.13 [0.85, 1.50]	0.42	0.94 [0.69, 1.27]	0.69
13-15	2174	1.44 [1.10, 1.88]	0.008	1.20 [0.91, 1.58]	0.19
≥16	2985	1.0		1.0	
IV drug use history at ALLRT enrollment					
Yes	757	1.27 [0.91, 1.76]	0.16	1.12 [0.80, 1.57]	0.51
No	6558	1.0		1.0	
History of AIDS defining illness at ALLRT enrollment					
Yes	1875	1.15 [0.90, 1.48]	0.27	-	-
No	5439	1.0		-	-
History of diabetes at ALLRT enrollment					
Yes	538	1.32 [0.90, 1.93]	0.15	-	-
No	6777	1.0		-	-

	Person years	Univariate		Multivariate	
		RR (95% CI) **	p-value	RR (95% CI) **	p-value
History of MI at ALLRT enrollment					
Yes	136	0.52 [0.17, 1.63]	0.26	-	-
No	7178	1.0		-	
History of stroke at ALLRT enrollment					
Yes	123	0.58 [0.19, 1.74]	0.33	-	-
No	7191	1.0		-	
Geographic location of the site					
North-east	1633	0.60 [0.42, 0.84]	0.003	0.67 [0.47, 0.96]	0.03
West	1452	0.98 [0.72, 1.34]	>0.9	1.03 [0.75, 1.42]	0.84
Mid-West	2303	0.76 [0.57, 1.02]	0.06	0.93 [0.68, 1.27]	0.63
South	1926	1.0		1.0	
Time-updated smoking history					
Yes	4488	1.15 [0.91, 1.46]	0.24	1.14 [0.89, 1.46]	0.31
No	2828	1.0		1.0	
Time-updated body mass index (kg/m ²)					
≥30	907	0.99 [0.69, 1.43]	>0.9	-	-
25-29	2733	0.98 [0.77, 1.25]	0.87	-	-
<25	3675	1.0		-	
Time-updated CD4+ T-cell count (cells/mm ³)					
≤350	2306	1.17 [0.92, 1.48]	0.28	-	-
>350	5009	1.0		-	
Time-updated HIV-1 RNA viral load (copy/ml)					
≥400	2065	1.76 [1.39, 2.21]	<0.001	1.52 [1.20, 1.93]	<0.001
<400	5249	1.0		1.0	
Time-updated ARV status*					
Off ARVs	830	2.54 [1.86, 3.46]	<0.001	-	-
On ARVs	6485	1.0		-	
Years since end of parent study					

	Person years	Univariate		Multivariate	
		RR (95% CI) **	p-value	RR (95% CI) **	p-value
Every 1 year increase		0.94 [0.90, 0.98]	0.003	0.95 [0.91, 1.00]	0.03

* By replacing time-updated viral load with time-updated ARV status in the final multivariate model, we obtain an adjusted RR (95%CI): 2.38 [1.73, 3.28], with p-value <0.001.

** RR (95%CI)= Relative risk (95% percent confidence interval)