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Journal

Clinical Infectious Diseases, 56(10)

ISSN

1058-4838

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Publication Date

2013-05-15

DOI

10.1093/cid/cit053

Peer reviewed

Effect of Statin Therapy in Reducing the Risk of Serious Non-AIDS-Defining Events and Nonaccidental Death

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Background. Excessive inflammation persists despite antiretroviral treatment. Statins decrease cardiovascular (CV) disease risk by reducing low-density lipoprotein cholesterol and inflammation. We performed an exploratory analysis to evaluate whether statin therapy decreased risk of non-AIDS-defining events and nonaccidental death.

Methods. A total of 3601 subjects not on a statin from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort were included. Outcome was time to first clinical event (CV event, renal or hepatic disease, incident diabetes, thrombotic/embolic event, nontraumatic fracture, non-AIDS-defining malignancy, serious bacterial infection, or nonaccidental death); event categories were also analyzed separately. Inverse probability of treatment and censoring weighted Cox proportional hazard models were used to assess the causal statin effect. Differential statin effects by baseline covariates were evaluated.

Results. Over 15 135 person-years (PY) of follow-up, 484 subjects initiated statins; 616 experienced an event (crude event rate, 4.4/100 PY on a statin and 4.1/100 PY not on a statin); the unadjusted hazard ratio (HR) was 1.17 (95% confidence interval [CI], .91–1.50). In a final weighted model, the adjusted HR (AHR) was 0.81 (95% CI, .53– 1.24). Results for other clinical events were similar, except for malignancies (AHR, 0.43 [95% CI, .19–.94]) and bacterial infections (AHR, 1.30 [95% CI, .64–2.65]). No differential statin effects by baseline covariates were detected.

Conclusions. Although statin therapy was not associated with a reduction in time to all non-AIDS-defining event or nonaccidental death, it was associated with a statistically significant 57% reduction in non-AIDS-defining malignancies. Confirmatory studies are needed to evaluate statin-associated reduction in risk of cancer and non-AIDS-associated morbidities.

Keywords. HIV infection; statins; ALLRT; inflammation; immune activation.

Despite the use of effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection is associated with inflammation and chronic immune activation, both of which have been independently associated with all-cause mortality [1–4]. Numerous studies support the hypothesis that inflammation contributes to increased risk of end-organ disease including cardiovascular disease, neurocognitive impairment, osteoporosis, malignancy, frailty, and liver disease [5–10].

Identifying interventions to diminish inflammation and its negative consequences remains of great interest [11, 12]. Statins have emerged as a potential adjunctive therapy for diseases with excess inflammation, including rheumatoid arthritis, nonalcoholic steatohepatitis, Alzheimer disease, and chronic hepatitis C virus (HCV) and HIV infection [13–17]. While lipid-lowering effects are touted widely, certain cholesterol-independent effects of statins may be advantageous for the mitigation of chronic inflammation: decreased hepatic production

Received 14 August 2012; accepted 24 January 2013; electronically published 5 February 2013.

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Clinical Infectious Diseases 2013;56(10):1471–9

DOI: 10.1093/cid/cit053

of interleukin 6, reduced lymphocyte and monocyte activation, improved nitric oxide synthesis, and anticoagulation effects [13]. Statins decrease T-cell activation in untreated HIV-infected persons and are being evaluated in persons with viral suppression [18].

We tested the hypothesis that HIV-infected persons reporting statin use have a decreased risk of end-organ disease and nonaccidental death in an exploratory retrospective analysis utilizing the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort (ClincalTrials.gov identifier: NCT00001137) to inform effect size, endpoints of interest, and specific populations for future trial development [19].

METHODS

Study Population

ALLRT is an observational cohort enrolling HIV-infected persons prospectively randomized to initiate ART, immune-based therapy, or ART strategies within ACTG parent studies [19]. The study was designed to evaluate long-term outcomes associated with ART, thus providing an ideal population to evaluate the effect of statins. After parent protocol completion, ALLRT follow-up continued at 16-week intervals. The June 2009 ALLRT datasets were used for these analyses. ALLRT and parent studies are approved by the institutional review board at each location; participants provide written informed consent for both.

Study Outcomes

The primary aim was to examine the effect of statin use on end-organ disease and nonaccidental death, after ALLRT entry. Outcomes of interest included major cardiovascular, renal or hepatic disease, incident diabetes, stroke, thrombotic event, nontraumatic fracture, non-AIDS-defining malignancy (all cancers excluding Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer), serious bacterial infection, or nonaccidental death from any cause similar to those defined in previous studies (Supplementary Appendix) [20]. Given concern regarding time for statins to have an effect and limited precision of statin start and stop dates in the ALLRT database, we excluded events from the 56 days after statin initiation. In a sensitivity analysis, these early events are included to evaluate for bias due to exclusion. In a post hoc analysis, we evaluated whether the impact of statin therapy varied by time since initiation, as well as its effect on AIDS-defining events collected in ALLRT [21].

Statistical Considerations

We utilized marginal structural model methodology [22, 23]. The hazard ratio (HR) of study outcomes for statin initiation vs noninitiation was estimated with pooled logistic model for risk of study outcomes at a given month, which included a time-varying indicator for use of statins through the preceding month and the following baseline covariates: age, sex, race/ethnicity, intravenous drug history, history of coronary artery disease, hepatitis B coinfection, systolic blood pressure (BP), estimated glomerular filtration rate (eGFR), serum glucose, low-density lipoprotein (LDL) cholesterol, current use of nonstatin lipid-lowering drugs, HIV type 1 (HIV-1) RNA, CD4 count, current smoking, and waist-to-hip ratio.

Statin initiation is more likely in subjects who smoke and have elevated LDL cholesterol and systolic BP, leading to time-dependent confounding by indication. Because these confounders are affected by prior statin use and are on the causal pathway between statins and study outcomes, we used inverse probability of treatment weighting (IPTW) to adjust for measured time-dependent confounders; inverse probability of censoring weighting (IPCW) was used to adjust for potential selection bias due to censoring. Both the statin initiation and censoring weights were stabilized and their products used in the final weighted regression model. Assuming that all time-varying predictors of both statin initiation or censoring and our study outcomes were included in the analyses, the weighted model estimates the parameters of a marginal structural Cox model [22–25].

All subjects in the logistic models received a time-varying weight inversely proportional to the probability of having their own observed history of statin initiation and history of censoring. To estimate each subject's probability of statin initiation or censoring at each month, separate pooled logistic models were used including covariates listed above plus the most recent value of time-varying covariates: systolic BP, eGFR, glucose, LDL cholesterol, current use of nonstatin lipid-lowering drugs, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio.

Following intent-to-treat principles, we assumed that subjects remain on statins once initiated. P values <.05 were interpreted as statistically significant. Nominal values were reported without adjustment for multiple comparisons. In a planned secondary analysis, we evaluated study outcomes by covariate stratification to look for a differential effect for baseline covariates. Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Of 4641 subjects in the 2009 ALLRT database, 4405 were not on a statin at ALLRT enrollment; 3601 had complete baseline data and were included. Compared to persons with incomplete baseline data, persons included in this analysis had statistically significant lower waist-to-hip ratio, higher glucose, higher

eGFR, less use of lipid-lowering drugs (not statins), lower CD4 cell count, lower Framingham risk score, later year of parent study entry, shorter time from parent study entry to ALLRT entry, and greater use of ART (data not shown).

At ALLRT entry, the study population was 83% male, 47% non-Hispanic white, 30% non-Hispanic black, and 21% Hispanic; 38% were current smokers, 21% had preceding AIDS-defining events; and median nadir and baseline CD4 counts were 180 cells/mm^3 and 346 cells/mm^3, respectively. Median LDL cholesterol was 106 mg/dL with 73% having a value <130 mg/dL. The median time from parent study entry to ALLRT entry was 16 weeks. Overall, 95% of persons were on ART (38% protease inhibitor based, 39% nonnucleoside reverse transcriptase inhibitor based, 23% other) with 66% having plasma HIV-1 RNA <400 copies/mL. Other baseline parameters are listed in Table 1.

Over 15 135 years of follow-up, 481 subjects initiated a statin (54% atorvastatin, 35% pravastatin, 11% other). As expected, certain baseline parameters (male sex, older age, higher LDL cholesterol, history of cardiovascular [CV] endpoint) and time-varying covariates (higher systolic BP, glucose, LDL cholesterol, waist-to-hip ratio, use of nonstatin lipid-lowering drugs, lower plasma HIV RNA level, higher CD4$^+$ T-cell count) were independently associated with a greater probability of statin initiation ($P < .05$ for all). The median (Q1, Q3) duration of follow-up since statin initiation in this cohort was 2.8 years (1.6, 4.9).

A total of 616 first non-AIDS events were observed (Table 2), 72 following statin initiation and 544 among subjects not on a statin (crude incidence rates, 4.4 and 4.0 events, respectively, per 100 person-years [PY]). In an unadjusted model, statin use was associated with a 17% increase in the hazard of events (HR, 1.17 [95% confidence interval {CI}, .91–1.50]). After weighting, statin use was associated with a 19% reduction in event rate (adjusted HR [AHR], 0.81 [95% CI, .53–1.24]; Figure 1).

To evaluate whether the observed statin effect was driven primarily by CV events, we repeated the analysis with these events removed and by individual event categories (Table 3). Consistent results were observed for CV events (AHR, 0.89 [95% CI, .32–2.44]) and non-CV events (AHR, 0.85 [95% CI, .56–1.31]). For the individual event categories of mortality, incident diabetes, and renal events, effect sizes of a similar magnitude to the overall effect were observed. Statin use was associated with a higher rate of bacterial infections (AHR, 1.25 [95% CI, .62–2.51]) and had a protective effect for malignancy of greater magnitude than the observed overall effect (AHR, 0.43 [95% CI, .19–.94]). With the exception of the analysis restricted to malignancies, the 95% CIs for all estimated effects include an HR of 1.

In planned subgroup analyses, evidence of a differential statin effect by baseline characteristics was evaluated (Figure 2). Although no differential effects were detected (P value for interaction >.1), some interesting trends were observed. For example, the estimated beneficial effect of statins increased with higher nadir CD4$^+$ T-cell count, older age, among females, and among black non-Hispanics.

To assess for bias by excluding events in the 56 days after statin initiation, we performed sensitivity analyses. Eight

Table 1. Baseline Characteristics of Participants (N = 3601)

Characteristic	Participants, No. (%)
Age, y, at ALLRT entry, median (Q1, Q3)	39 (33, 46)
Male sex	3006 (83%)
Race/ethnicity	
Black non-Hispanic	1070 (30%)
White non-Hispanic	1686 (47%)
Hispanic (regardless of race)	748 (21%)
BMI, kg/m^2, median (Q1, Q3)	25.0 (22.6, 28.0)
Current smoker	1383 (38%)
Self-reported health	
Very good/excellent	1937 (54%)
Good	1095 (31%)
Poor/fair	526 (15%)
Not reported	43
BP, mm Hg, median (Q1, Q3)	120 (110, 130)/76 (70, 82)
LDL cholesterol, mg/dL, median (Q1, Q3)	106 (83, 131)
LDL cholesterol <130 mg/dL	2640 (73%)
Framingham Risk Score >10%	361 (10%)
Hepatitis C virus antibody reactive	354 (10%)
Hepatitis B virus surface antigen reactive	117 (3%)
On ART at ALLRT enrollment	3438 (95%)
Protease inhibitor based	1309
NNRTI based	1327
Other	802
Plasma HIV RNA, copies/mL, median (Q1, Q3)	<400 (<400, 5080)
Baseline CD4 count, copies/mm^3, median (Q1, Q3)	346 (204, 508)
Nadir CD4 count, copies/mm^3, median (Q1, Q3)	180 (60, 291)
Nadir CD4 count <200 copies/mm^3	1952 (54%)
AIDS-defining event prior to ALLRT	757 (21%)
Year of parent study entry	
1997–1999	1018 (28%)
2000–2002	804 (22%)
2003–2005	845 (23%)
2006–2007	934 (26%)
Time, wk, from parent study enrollment to ALLRT, median (Q1, Q3)	16 (7, 60)

Abbreviations: ALLRT, AIDS Clinical Trials Group Longitudinal Linked Randomized Trials; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor.

Table 2. Summary of First Event

Event Category	First Event Within Category, No.	First Event Overall, No.
Incident diabetes	158	144 (23.4%)
Serious bacterial infection	144	124 (20.1%)
Pneumonia	120	106
Sepsis	18	11
Bacterial bronchitis	5	5
Bacterial meningitis	1	1
Renal	135	115 (18.7%)
Malignancy	89	81 (13.2%)
Anorectal cancer	14	13
Lung cancer	13	12
Hodgkin lymphoma	10	10
Prostate cancer	8	7
Hepatic cancer	6	6
Oropharyngeal cancer	6	6
Genitourinary cancer	4	4
Malignant melanoma	4	4
Colon cancer	3	3
Gastric/small intestine cancer	4	3
Breast cancer	4	2
Thyroid cancer	2	2
Other	11	7
Mortality	143	76 (12.3%)
Cardiovascular	62	42 (6.8%)
Myocardial infarction	36	24
Stroke	19	12
Transient ischemic attack	6	5
Carotid artery stenosis	1	1
Thrombosis/embolism	22	17 (2.8%)
Pulmonary embolus	14	12
Deep venous thrombosis	8	5
Hepatic	11	9 (1.5%)
Fragility fracture	8	8 (1.3%)
Wrist	5	5
Hip	2	2
Lumbar spine	1	1
Total	NA	616 (100%)

Abbreviation: NA, not applicable.

additional events were included in the statin group (3 CV, 3 incident diabetes, 1 death, 1 renal). For the primary composite endpoint, there was a shift in the AHR from 0.81 (95% CI, .53–1.24) to 0.88 (95% CI, .58–1.35; Table 4).

In a post hoc analysis, the AHR was estimated as a function of time since statin initiation, utilizing a 3-level time-varying indicator (ie, no statin, <2 years after initiation, ≥2 years after initiation). Although the AHR was not statistically different ($P = .20$) by category, there was a shift in effect (<2 years: 0.96 [95% CI, .58–1.59]; ≥2 years: 0.63 [95% CI, .37–1.06]). We also assessed the impact of statin initiation on AIDS-defining events. There were 172 AIDS-defining events, with *Pneumocystis jirovecii* pneumonia (n = 31), esophageal candidiasis (n = 26), disseminated mycobacterial infection other than tuberculosis (n = 17), wasting syndrome (n = 17), Burkitt lymphoma (n = 16), and cryptosporidiosis (n = 16) being the most common (Table 5). Crude event rates were 1.1 per 100 PYs off statin and 0.5 per 100 PYs on statins (crude HR, 0.80 [95% CI, .43–1.50]). After modeling, with IPTW and IPCW, there was a 24% increase in event rate (AHR, 1.24 [95% CI, .44–3.52]) with the use of statins.

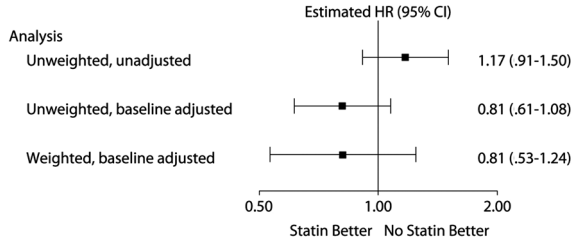

Figure 1. Primary analysis: effect of statins on time to first event. Abbreviations: CI, confidence interval; HR, hazard ratio.

DISCUSSION

Overall, statin use was associated with a 19% reduction in non-AIDS events and nonaccidental mortality, although this finding was not statistically significant. Most striking was a 57% reduction in malignancy risk associated with statin use. The beneficial effects of statins were not driven specifically by CV events, providing plausibility that statins have important anti-inflammatory properties providing benefit beyond CV prevention. However, for serious bacterial infection, statins were associated with a nonsignificant 25% increased risk.

Interestingly, event rates for non-AIDS events were nearly 4 times higher than for AIDS-defining events (4.1 vs 1.1 per 100 PY). The higher incidence of non-AIDS-defining events supports other reports that non-AIDS events are increasingly relevant [26]. Palella et al reported a marked shift in causes for mortality: AIDS-related mortality declined from 54% to 25% and non-AIDS causes increased from 13% to 43% between 1996 and 2004 [27]. From the Strategies for Management of Antiretroviral Therapy (SMART) and Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) studies, similar findings have been reported: serious non-AIDS events occurred nearly 50% more frequently than AIDS-defining events, with a demonstrably higher mortality rate at 6 months for non-AIDS-related causes (13% vs 5%) [28].

The differences in risk for endpoint categories are intriguing. Notably, the risk for bacterial infections and AIDS-

Table 3. Event Rates for Different Categories

Event Category	No. of Events	Event Rate for Statin Users (per 100 PY)	Event Rate for Nonstatin Users (per 100 PY)	Crude HR (95% CI)	Baseline Adjusted[a] HR (95% CI)	Adjusted[a] and Weighted[b] HR (95% CI)
CV events	62	0.5	0.4	1.44 (.72–2.88)	0.82 (.35–1.92)	0.89 (.32–2.44)
Non-CV events	580	4.2	3.8	1.18 (.93–1.55)	0.82 (.62–1.09)	0.85 (.56–1.31)
Bacterial infections	144	0.7	0.9	0.96 (.56–1.66)	0.96 (.54–1.71)	1.25 (.62–2.51)
Incident diabetes	158	1.3	1.0	1.52 (.95–2.44)	1.02 (.59–1.76)	0.87 (.35–2.13)
Renal events	135	1.4	0.7	1.58 (1.00–2.49)	1.00 (.59–1.71)	0.85 (.41–1.73)
Malignancies	89	0.5	0.5	1.03 (.52–2.03)	0.71 (.36–1.37)	0.43 (.19–.94)
Mortality	143	0.5	0.9	0.47 (.25–.91)	0.41 (.20–.85)	0.82 (.32–2.10)
AIDS-defining events	172	0.5	1.1	0.80 (.43–1.50)	0.84 (.42–1.68)	1.24 (.44–3.52)

Abbreviations: BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio; PY, person-years.

[a] Adjusted for the following baseline covariates: age, sex, race/ethnicity, intravenous drug history, history of coronary artery disease (CAD), hepatitis B coinfection, systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio.

[b] Weights based on the following baseline covariates: age, sex, race/ethnicity, intravenous drug history, history of CAD, hepatitis B coinfection, systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio; and the following time-varying covariates: systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio.

defining events appeared to be increased with statin initiation. It is possible that this association was driven by nonadherence to both HIV and statin therapy and thus progressive HIV disease, but it is certainly possible that statin-induced reductions in innate immune activation might have beneficial effects on some morbidities, yet harmful effects on clearance

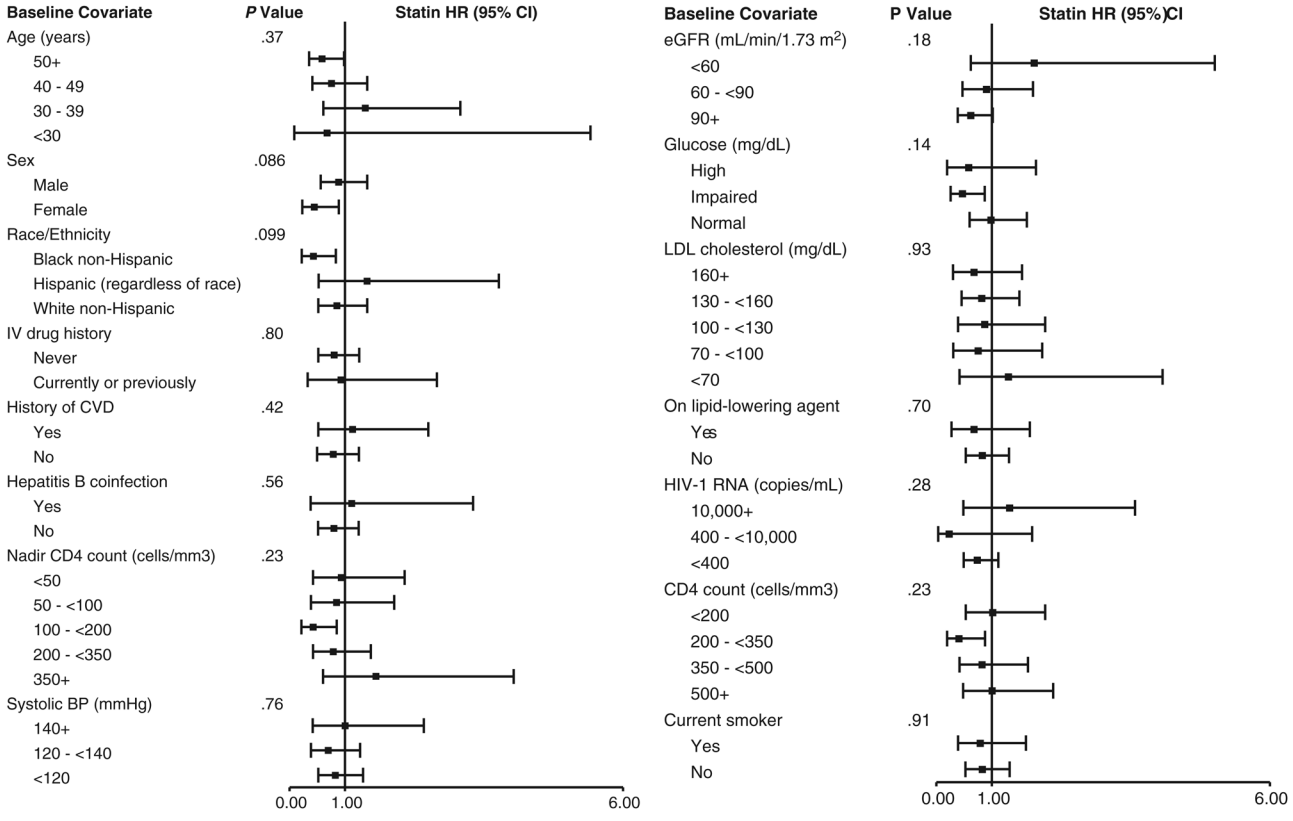

Figure 2. Differential effect by baseline covariates. Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio; IV, intravenous; LDL, low-density lipoprotein.

Table 4. Sensitivity Analysis Including Early Events

Event Category	No. of Events	Adjusted[a] and Weighted[b] HR (95% CI)	No. of Events[c]	Adjusted[a] and Weighted[b] HR[c] (95% CI)
CV events	62	0.89 (.32–2.44)	65	0.90 (.35–2.30)
Non-CV events	580	0.85 (.56–1.31)	583	0.91 (.59–1.40)
Bacterial infections	144	1.25 (.62–2.51)	144	1.30 (.64–2.65)
Incident diabetes	158	0.87 (.35–2.13)	159	0.91 (.36–2.29)
Renal events	135	0.85 (.41–1.73)	136	0.93 (.45–1.92)
Malignancies	89	0.43 (.19–.94)	90	0.43 (.21–1.05)
Mortality	143	0.82 (.32–2.10)	144	0.87 (.34–2.23)

Abbreviations: BP, blood pressure; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio.

[a] Adjusted for the following baseline covariates: age, sex, race/ethnicity, intravenous drug history, history of coronary artery disease (CAD), hepatitis B coinfection, systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio.

[b] Weights based on the following baseline covariates: age, sex, race/ethnicity, intravenous drug history, history of CAD, hepatitis B coinfection, systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio; and the following time-varying covariates: systolic BP, eGFR, glucose, current use of lipid-lowering drugs other than statins, HIV-1 RNA, CD4 count, current smoking, and waist-to-hip ratio.

[c] Including early events.

Table 5. Summary of AIDS-Defining Events

Event Category	Events, No. (%)
Pneumocystis jirovecii pneumonia	31 (18.0)
Esophageal candidiasis	26 (15.1)
Disseminated mycobacterial infection (not tuberculosis)	17 (9.9)
HIV wasting	17 (9.9)
Cryptosporidiosis	16 (9.3)
Non-Hodgkin lymphoma	16 (9.3)
Kaposi sarcoma	9 (5.2)
Bacterial pneumonia (2 events in a 12-mo period)	8 (4.7)
Tuberculosis	6 (3.5)
Cerebral toxoplasmosis	5 (2.9)
Cryptococcosis	5 (2.9)
Cytomegalovirus disease	5 (2.9)
Herpes simplex virus disease	5 (2.9)
Cervical cancer	2 (1.2)
Progressive multifocal leukoencephalopathy	1 (0.6)
Disseminated histoplasmosis	1 (0.6)
Isosporiasis	1 (0.6)
HIV-associated dementia	1 (0.6)
Total	172 (100)

Abbreviation: HIV, human immunodeficiency virus.

of infections in the setting of immunodeficiency. Previous reports in HIV-uninfected persons have suggested that bacterial infections, particularly bacterial pneumonia, are reduced with statin therapy mediated through reduction in immune activation and inflammatory cytokines [29]. The effects of statins may serve to attenuate an overexuberant immune response to pathogens. Future research should explore whether the depletion of CD4 cells with HIV infection may alter the signaling pathways through which statins affect immune surveillance and negatively impact infections [13, 30].

In the geriatrics literature, immunosenescence contributes to progression of end-organ disease, characterized by a proinflammatory state manifested by a phenotype of T-cell exhaustion, elevated proinflammatory cytokine levels, and poor responses to recall or neoantigens [31, 32]. This shift contributes to functional decline with accrual of comorbidities and increased mortality. HIV infection causes persistent inflammation and T-cell activation with a heightened risk for non-AIDS comorbidities [4]. In the pre–highly active antiretroviral therapy era, Giorgi et al demonstrated that T-cell activation contributes significantly to mortality [33]. Subsequent data from numerous groups have demonstrated that ART reduces the level of inflammation and T-cell activation to some degree but incompletely [1, 34]. The residual proinflammatory state is associated with end-organ disease and mortality [2–4, 35]. Recently published data demonstrated that atorvastatin significantly reduced T-cell activation in untreated HIV-infected persons, similar to previous reports in HIV-uninfected persons [19, 36].

Another retrospective analysis highlighted a 3-fold reduction in hazard of death in individuals with suppressed viremia who received a statin [37]. In our analysis, we reported very similar results after adjusting for baseline parameters, demonstrating a 59% reduction in mortality (AHR, 0.41). After the weighting for time-varying covariates, the AHR shifted to 0.82, indicating an 18% reduction.

Another observational study demonstrated a 45% reduction in risk of non-Hodgkin lymphoma for those individuals who received a statin [38]. These data are consistent with our data, which demonstrated a 57% reduction in malignancies. For many malignancies, inflammation and altered immune function are important contributors, and in the case of HIV have been linked to the incidence of lymphoma [39, 40]. Although it is difficult to generalize given the broad number of cancers included in this analysis, recognition that immune dysfunction and persistent inflammation may contribute to development of malignancies speaks to the need to investigate preventative therapies to abrogate the development of these events.

Although reduction in overall events did not reach statistical significance, these data inform future trial development. In particular, identifying event rates and effect size in particular demographic groups from this analysis will influence future trials. For instance, statin therapy modestly reduced events in persons <30 years of age (19% reduction) whereas persons >50 experienced a 51% reduction of non-AIDS events. Given that non-AIDS event rates are higher in older persons, a meaningful result could be achieved with a smaller sample in that particular population. For example, limiting a study to include HIV-infected persons >45 years with LDL cholesterol <130 mg/dL (in whom the event rate was 8.2/100 PY in this analysis), a sample size of 2900 participants would provide 90% power to detect a 20% reduction in events. This 20% reduction would be highly relevant, as the number needed to treat to prevent 1 event over 5 years would be 17.

The current analysis has certain limitations. To address the potential for confounding by indication, which inherently biases treatment effects detected in observational trials, we utilized marginal structural modeling (MSM). Treatment and censoring weights were used to create a pseudopopulation whereby the probability of initiating a statin or being censored was unrelated to measured time-dependent confounders. As these time-dependent confounders are controlled for by the weights rather than by inclusion as covariates, we minimize the concern that these confounders serve as intermediates on the causal pathway from statin initiation to study outcomes. MSM attempts to estimate the causal effect of statins, rather than simply present associations, based upon certain assumptions. First, the methodology assumes that no unmeasured confounding was present and thus the inverse probability weights adjust for both confounding and selection bias. This assumption relies on accurate data on all time-dependent confounders. We acknowledge that this untestable assumption may not fully hold and some residual unmeasured confounding may exist. However, the baseline and time-varying covariates, which were identified as independently associated with statin initiation, are the factors we would expect to identify in this population. Second, the methodology assumes that reporting of statin initiation and study outcomes are accurate. Although data for common CV risk factors (smoking status, fasting lipid panel, and BP) were prospectively collected at ALLRT visits, data for other parameters were not collected, such as antiplatelet therapies or cytomegalovirus status. Also, because our analyses are restricted to data collected after ALLRT enrollment, underreporting for some events may have occurred due to recall bias. Additionally, the set of covariates we used to address confounding may not be the minimal set needed. Adjusting for too many covariates may introduce bias or substantially increase the variance of the treatment effect while adjusting for too few may not fully resolve the issue of confounding [25]. Also, 18% of potential ALLRT subjects with missing baseline data were not included. Of the 3601 subjects included in the analysis population, 616 (17%) first events were reported; for the 804 subjects not included, there were 158 (20%) first events. Additionally, 13% of the analysis subjects initiated a statin, whereas 20% of subjects not included initiated a statin. It is difficult to speculate whether exclusion of these 804 subjects may have biased our results, if at all, due to the reliance of the treatment and censoring weights on baseline data. In the absence of a randomized clinical trial, and despite these limitations, we believe that the use of MSM methodology within the ALLRT cohort provides the optimal opportunity to estimate the causal effect of statin initiation.

Exclusion of early events was aimed at preventing misclassification due to challenges with reporting events and the exact timing of statin initiation. We recognized the potential impact on our results and performed a sensitivity analysis to include early events. Eight events were identified and included in this analysis, some of which were reported within days of statin initiation. The inclusion of these events caused minor shifts in AHR point estimates and 95% CIs. Results were not markedly different from the initial analysis, indicating that results are not overly biased by timing of events.

We were potentially underpowered to detect all but large statin effects. In preparation for the analysis, we estimated that with 4500 persons, of whom 30% initiated a statin, and an event rate of 1.9 per 100 PY in the nonstatin group, we would have 80% power to detect a 26% difference in event rates. In the restricted cohort with complete baseline data that was ultimately included, only 13% initiated a statin. Although the observed event rate in the nonstatin group was higher than anticipated (4.0 per 100 PY), this reduction in sample size and the loss of efficiency associated with the weighting likely contributed to the wide confidence intervals seen.

In summary, statins were associated with a 19% reduction in non-AIDS events and nonaccidental death that was not statistically significant. Malignancies were the only endpoint for which a statistically significant reduction in event rate was observed. The benefits of statins were more apparent in the older population. Our results inform the future development of properly sized prospective clinical endpoint trials to reduce residual inflammation despite ART and limit the development of non-AIDS comorbidities.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. The project described was supported by the National Institute of Allergy and Infectious Diseases (U01AI068636), the National Institute of Mental Health, and the National Institute of Dental and Craniofacial Research. E. T. O. is supported by the University of Alabama at Birmingham Center for AIDS Research (P30 AI027767).

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

Potential conflicts of interest. E. T. O. has served as a consultant for ViiV Pharmaceuticals. P. W. H. has served as a consultant for Merck and has served on the speakers' bureaus for Gilead and Janssen. J. H. S. receives royalties from a patent with the Wisconsin Alumni Research Foundation and has served on data safety monitoring committees for Abbott, Lilly, and Takeda. P. T. has served as a consultant for Merck, GlaxoSmithKline, and Cytheris and receives royalties from UpToDate. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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