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## Low density lipoprotein cholesterol response after statin initiation among persons living with HIV

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## Abstract

**Background:** Meta-analyses of general population studies report mean low density lipoprotein cholesterol (LDL-C) reductions of 30% to <50% with moderate-intensity and 50% with high-intensity statins. Persons living with HIV (PLWH) are at high risk for atherosclerotic cardiovascular disease (ASCVD) yet many have elevated LDL-C.

**Objective:** To evaluate LDL-C response following statin initiation among PLWH.

**Methods:** We conducted a retrospective cohort study of PLWH initiating statins between 2009 and 2013 (N=706). Patients were categorized into mutually exclusive groups in the following hierarchy: history of coronary heart disease (CHD), diabetes, pre-statin LDL-C  $\geq$  190 mg/dL, 10-year predicted ASCVD risk  $\geq$  7.5%, and none of the above (i.e., unknown statin indication). The primary outcome was a  $\geq$  30% reduction in LDL-C following statin initiation.

**Results:** Among patients initiating statins, 5.8% had a history of CHD, 13.6% diabetes, 6.2% LDL-C  $\geq$  190 mg/dL, 35.4% 10-year ASCVD risk  $\geq$  7.5%, and 39.0% an unknown statin indication. Among patients with a history of CHD, 31.7% achieved a  $\geq$  30% LDL-C reduction, compared to 25.0%, 59.1%, and 33.9% among those with diabetes, LDL-C  $\geq$  190 mg/dL, and 10-year ASCVD risk  $\geq$  7.5% respectively. In multivariable-adjusted analyses and compared to patients with an unknown statin indication, LDL-C  $\geq$  190 mg/dL was associated with a prevalence ratio for an LDL-C reduction  $\geq$  30% of 1.81 (95% confidence interval 1.34–2.45), whereas no statistically significant association was present for history of CHD, diabetes, and 10-year ASCVD risk  $\geq$  7.5%.

**Conclusion:** A low percentage of PLWH achieved the expected reductions in LDL-C after statin initiation, highlighting an unmet need for ASCVD risk reduction.

## Keywords

HIV-infection; statin; dyslipidemia; low density lipoprotein cholesterol; cardiovascular disease

## INTRODUCTION:

Meta-analyses of general population studies have demonstrated mean reductions in low density lipoprotein cholesterol (LDL-C) of 30% to <50% with moderate-intensity statins and 50% with high-intensity statins.<sup>1</sup> The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline has identified four groups of patients for whom the benefit of statins in reducing risk of atherosclerotic

cardiovascular disease (ASCVD) outweighs the risk for adverse effects: clinical ASCVD, diabetes, LDL-C  $\geq 190$  mg/dL, or 10-year predicted ASCVD risk  $\geq 7.5\%$ .

Persons living with human immunodeficiency virus (PLWH) have been identified by the National Lipid Association as a population at high risk for ASCVD.<sup>2</sup> Among PLWH, risk for coronary heart disease (CHD) and cerebrovascular disease is 1.5 to 2-fold higher compared to uninfected individuals.<sup>3</sup> Dyslipidemia is more common among PLWH than uninfected persons with low high density lipoprotein cholesterol (HDL-C) and elevated triglycerides being the most common abnormalities.<sup>2</sup> However, use of statins in PLWH is complex; while PLWH are at increased risk for ASCVD, they also have an increased risk for drug-drug interactions and for comorbidities including chronic kidney disease (CKD) or liver disease.<sup>4</sup> This situation is further complicated by a lack of large randomized clinical trials of statins among PLWH. The 2013 ACC/AHA cholesterol treatment guideline emphasizes the importance of clinical judgment in balancing the benefits versus risks in PLWH with regards to use of statins to reduce ASCVD risk.<sup>1</sup>

Prior studies have demonstrated poor control of dyslipidemia among PLWH taking statins.<sup>5–10</sup> However, there is a paucity of data on LDL-C reduction following initiation of statin therapy among PLWH in routine clinical care. Determining the mean LDL-C reduction following the initiation of statin therapy among PLWH may inform healthcare provider decisions on how to improve dyslipidemia management and ASCVD risk reduction.

The objective of this study was to determine the LDL-C response to initiating statins among adults with human immunodeficiency virus (HIV), with a primary outcome of a 30% reduction in LDL-C. To achieve this objective, we analyzed data from the multi-site Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort from 2009 to 2013. Although much of the study period occurred under the Adult Treatment Panel (ATP III) guideline for cholesterol management, we chose to evaluate LDL-C response using the 2013 ACC/AHA cholesterol treatment guideline.<sup>1, 11</sup> This approach is more meaningful in determining areas for improvement in cholesterol management and ASCVD risk reduction among PLWH. Also, we determined the percentage of PLWH who achieved LDL-C targets of  $<70$  and  $<100$  mg/dL following initiation of statin therapy.

## MATERIAL AND METHODS:

### Study design and setting:

This retrospective study was conducted within CNICS, a cohort of adult PLWH receiving primary care at eight academic HIV clinical sites across the United States.<sup>12</sup> CNICS was initiated in 1995 and since that time has maintained a centralized data repository with detailed demographic, clinical, and behavioral data on approximately 32,000 patients. Seven of the eight CNICS sites contributed data to this study (University of Alabama at Birmingham, University of Washington, Johns Hopkins University, University of California San Diego, University of California San Francisco, Fenway Community Health Center in Boston, MA, and University of North Carolina at Chapel Hill). Collection of data for CNICS was approved by the Institutional Review Board at each site. The University of Alabama

at Birmingham Institutional Review Board approved the current analysis of de-identified CNICS data.

### Eligibility criteria

For the current analysis, participants were selected in annual cohorts from 2009 through 2013 (Figure 1). For each calendar year, patients who met the following criteria were considered to have initiated a statin: 1) age ≥ 18 years on January 1; 2) at least 1 primary care visit in the calendar year; 3) statin use in the calendar year documented in their medical record; and 4) no statin use in the 24 months prior to the first documented statin use in the calendar year. Patients were required to have at least three visits in the 24 months prior to statin initiation, with at least one of these visits ≥ 6 months prior to statin initiation. This allowed for a 6- to 24-month period of observation that was used to confirm patients were not previously taking a statin. Patients who died in the same calendar year they initiated a statin were excluded. Patients who lacked a pre-statin LDL-C measurement in the period 12 months prior to statin initiation or a post-statin LDL-C measurement in the period 3 to 18 months after statin initiation were excluded. In addition, patients for whom statin discontinuation was reported preceding the date of their post-statin LDL-C measurement closest to 12 months after statin initiation were excluded. Patients who met the eligibility criteria in multiple calendar years were only included one time, for the earliest year under study. Among 18,898 CNICS patients age ≥ 18 years who were seen by a primary care provider during the study period, 931 initiated statins and had pre- and post-statin LDL-C measures; 225 (24.2%) had discontinued this treatment by the time of their post-statin LDL-C measurement. These patients were excluded from our analyses. Discontinuation reasons are not available in CNICS. The remaining 706 patients who were still taking a statin at the time of the post-statin LDL-C measurement were included in analyses evaluating LDL-C response. Among CNICS patients, 996 who initiated statins had available pre- and post-statin non-HDL-C measurements; 744 of these patients were still taking a statin at the time of the post-statin non-HDL-C measurement and were included in analyses evaluating non-HDL-C response.

### Sources of data

Data from inpatient and outpatient encounters are collected by CNICS sites at the point of care and retrieved from their electronic health records (EHRs) and other data systems. These data elements include demographic characteristics, diagnoses, procedures, medications, laboratory values, vital signs, and health care utilization.<sup>12, 13</sup> Sites submit these data to the CNICS Data Management Core at the University of Washington quarterly. Myocardial infarctions were adjudicated as previously described.<sup>14</sup> In addition, CNICS patients complete a self-administered computerized tobacco use questionnaire every 4–6 months.<sup>15</sup>

### Statin indication

Patients were categorized into mutually exclusive groups based on their indication for statin treatment according to the 2013 ACC/AHA cholesterol treatment guideline.<sup>1</sup> Categories were assigned based on patient characteristics prior to statin initiation and according to the following hierarchy: history of coronary heart disease (CHD) including MI or coronary

revascularization (percutaneous coronary intervention or coronary artery bypass grafting), diabetes but no history of CHD, no history of CHD or diabetes but with an LDL-C

190mg/dL based on the measurement most proximal to, and preceding, statin initiation, and no history of CHD or diabetes, with an LDL-C<190 mg/dL and with a 10-year predicted CVD risk  $\geq 7.5\%$ . Patients who did not have any of these indications identified were categorized as having an unknown indication for statin initiation. Diabetes was defined by a previous diagnosis of type 1 or type 2 diabetes and 1) laboratory confirmation (any history of hemoglobin A1c value  $\geq 6.5\%$  or two or more random blood glucose measurements  $\geq 200$  mg/dL in the 24 months prior to statin initiation), or 2) documented use of an antidiabetes medication in the 24 months prior to statin initiation. The Pooled Cohort risk equations were used to calculate 10-year CVD risk.<sup>16</sup>

## Outcomes

The primary outcome was achievement of an LDL-C reduction  $\geq 30\%$  after statin initiation. Secondary outcomes included  $\geq 50\%$  reduction in LDL-C and  $\geq 30\%$  and  $\geq 50\%$  reductions in non-high density lipoprotein cholesterol (non-HDL-C). Additional secondary outcomes included achieving an LDL-C  $<70$ mg/dL and  $<100$  mg/dL and a non-HDL-C  $<100$  mg/dL and  $<130$  mg/dL after statin initiation. Lipid values were obtained from routine laboratory results performed in the course of clinical care. Fasting status was not specified for the majority of lipid values. We calculated non-HDL-C as total cholesterol minus HDL-C. The pre-statin lipid values were defined using the measurement closest to but preceding statin initiation. We used the post-statin lipid values most proximal to 12 months after statin initiation, within a range of 3 to 18 months following initiation, to allow time for titration of the statin dose. The median time from statin initiation to the post-statin LDL-C measurement used was 349 days. In addition, we performed sensitivity analyses restricted to patients with lipid values in the one to three months after statin initiation.

## Independent variables

Variables of interest included age, sex, race/ethnicity, body mass index (BMI), estimated glomerular filtration rate (eGFR), use of HIV antiretroviral (ARV) therapy containing protease inhibitors (PIs) or cobicistat, CD4 count, plasma HIV-1 RNA, chronic hepatitis C virus (HCV), hypertension, self-reported smoking status, statin intensity upon treatment initiation, and use of non-statin lipid-lowering therapy at baseline. Variable definitions are given in Supplemental Table 1. Values for clinical characteristics were based on the date of statin initiation. If no value was available on that date, the value most proximal to, but preceding, the date of statin initiation was used. If no value was available within 12 months prior to statin initiation, it was considered missing.

## Statistical analysis

Characteristics of patients initiating statins were calculated overall and stratified by treatment indication (history of CHD, diabetes, LDL-C  $\geq 190$  mg/dL, 10-year predicted ASCVD risk  $\geq 7.5\%$ , and unknown statin indication). The proportion of each treatment indication group initiated on high-, moderate-, and low-intensity statins was calculated.

Mean absolute and percent LDL-C and non-HDL-C change, the proportion of patients achieving LDL-C and non-HDL-C reductions 30% and 50% from before to after statin initiation, and the percentages of patients achieving LDL-C targets of <70 mg/dL and <100 mg/dL and non-HDL-C targets <100 mg/dL and <130 mg/dL after statin initiation were calculated, stratified by statin indication. We calculated the number and proportion of patients taking individual statin type/dose combinations, and the proportion of patients taking each statin type/dose combination who achieved a 30% and 50% reduction in LDL-C. Next, we calculated univariate and multivariable adjusted prevalence ratios (PR) for achieving 30% reduction in LDL-C and non-HDL-C associated with statin indication. Patients with an unknown statin indication served as the referent group. The multivariable model included adjustment for age, sex, race/ethnicity, BMI, eGFR, use of PIs or cobicistat, CD4 count, plasma HIV-1 RNA, chronic HCV, hypertension, current smoking, statin intensity and use of non-statin lipid-lowering therapy. To account for the possibility of non-persistence among patients who appeared to be taking a statin at the time of their post-statin LDL-C and non-HDL-C measurements closest to 12 months after statin initiation, sensitivity analyses were performed calculating the proportion of patients with lipid measurements in the period one to three months after statin initiation who achieved a 30% and 50% reduction in LDL-C and non-HDL-C. To address missing data, we used multiple imputation with chained equations to create 10 datasets. The percentages of patients missing each variable used in the analyses are listed in Supplemental Table 2. Data analysis was conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Statin indication and intensity

Among 706 patients initiating statins and included in our analyses on LDL-C response, 5.8% had a history of CHD, 13.6% had diabetes, 6.2% had LDL-C  $\geq$  190 mg/dL, and 35.4% had 10-year predicted CVD risk  $\geq$  7.5%. The statin indication was unknown for the remaining 39.0% of patients. Patient characteristics are provided in Table 1. Overall, 15.2% of patients initiating statins were taking a fibrate at baseline, including approximately one-quarter of patients with diabetes or a history of CHD. Most of these patients were taking fenofibrate (78.5%) and 18.7% were taking gemfibrozil. Providers initiated high-, moderate-, and low-intensity statins for 9.8%, 65.9%, and 24.3% of patients respectively. Between 2009 and 2013, there was a small increase in the percentage of patients initiating treatment with a high-intensity statin and a small decline in the percentage of patients initiating treatment with moderate- and low-intensity statins (Supplemental Figure 2). Patients with history of CHD were more likely to initiate a high-intensity dosage compared to patients with other indications for initiating statin treatment (Figure 2). In terms of statin type, most patients initiated statin treatment with atorvastatin (39.7%), pravastatin (36.0%), and rosuvastatin (19.8%), whereas only a small percentage of patients initiated treatment with fluvastatin, lovastatin, or simvastatin, and none were taking pitavastatin. The percentage of patients achieving a 30% and 50% reduction in LDL-C stratified by statin type/dose is provided in Supplemental Table 3.

## LDL-C response

The mean change in LDL-C after statin initiation was  $-28.2$  (standard deviation [SD]:  $36.6$ ) mg/dL or  $-17.3\%$  (SD:  $28.0\%$ ). The absolute and percent change in LDL-C was larger among patients with pre-statin LDL-C  $\geq 190$  mg/dL compared to those with other indications for initiating statin therapy (Table 2). Among the overall population,  $34.4\%$  of patients achieved a reduction in LDL-C  $\geq 30\%$  and  $7.1\%$  achieved a reduction  $\geq 50\%$  following statin initiation. The proportion of patients achieving an LDL-C reduction  $\geq 30\%$  ranged from  $25.0\%$  for those with diabetes to  $59.1\%$  for those with a pre-statin LDL-C  $\geq 190$  mg/dL. The proportion of patients achieving an LDL-C reduction  $\geq 50\%$  ranged from  $4.4\%$  for those with unknown statin indication to  $20.5\%$  for those with a pre-statin LDL-C  $\geq 190$  mg/dL. Among patients initiating a high-intensity statin dose, the mean change in LDL-C was  $-31.5$  (SD:  $44.3$ ) mg/dL and  $-18.5\%$  (SD:  $31.8\%$ );  $35.6\%$  had an LDL-C reduction  $\geq 30\%$  and  $14.8\%$  had an LDL-C reduction of  $\geq 50\%$  (Supplemental Figure 1). Among patients initiating a moderate-intensity statin dose, the mean change in LDL-C was  $-29.9$  (SD:  $36.1$ ) mg/dL and  $-18.4\%$  (SD:  $28.0\%$ );  $36.6\%$  had an LDL-C reduction  $\geq 30\%$  and  $7.1\%$  had an LDL-C reduction of  $\geq 50\%$ .

## Patient characteristics associated with $\geq 30\%$ reduction in LDL-C

After multivariable adjustment, patients with a pre-statin LDL-C  $\geq 190$  mg/dL were more likely to have a  $\geq 30\%$  reduction in LDL-C compared with their counterparts for whom the statin indication was unknown (Table 3). Diabetes, history of CHD, and 10-year predicted ASCVD risk  $\geq 7.5\%$  were not associated with having a  $\geq 30\%$  LDL-C reduction after multivariable adjustment. Being overweight versus normal weight and having an eGFR  $<30$  versus  $\geq 60$  mL/min/1.73m<sup>2</sup> were also associated with a higher likelihood of having a  $\geq 30\%$  LDL-C reduction. African Americans were less likely than whites to have a  $\geq 30\%$  LDL-C reduction.

## Non-HDL-C response

Among 744 patients initiating statins and included in our analysis on non-HDL-C response, the mean change in non-HDL-C was  $-31.9$  (SD:  $44.1$ ) mg/dL or  $-15.6\%$  (SD:  $25.9\%$ ) following statin initiation, and  $29.6\%$  and  $3.2\%$  of patients had a non-HDL-C reduction of  $\geq 30\%$  and  $\geq 50\%$ , respectively. Among the statin indication groups, the largest absolute and percent change in non-HDL-C after statin initiation occurred among patients with pre-statin LDL-C  $\geq 190$  mg/dL (Supplemental Table 4). In multivariable adjusted analysis, patients with LDL-C  $\geq 190$  mg/dL versus those with unknown statin indication and those who were overweight versus normal weight were more likely to have a  $\geq 30\%$  reduction in non-HDL-C (Supplemental Table 5). African Americans were less likely to have a  $\geq 30\%$  reduction in non-HDL-C compared to whites.

## LDL-C and non-HDL-C targets

Overall  $12.6\%$  of patients achieved a post-statin LDL-C  $<70$  mg/dL, ranging from none of the patients with pre-statin LDL-C  $\geq 190$  mg/dL to  $34.1\%$  of those with history of CHD (Table 2). A post-statin LDL-C  $<100$  mg/dL was achieved by  $45.6\%$  of patients, ranging from  $11.4\%$  of those with a pre-statin LDL-C  $\geq 190$  mg/dL to  $73.2\%$  of those with history



of CHD. Overall 12.8 % of patients achieved a post-statin non-HDL-C <100 mg/dL, ranging from none of the patients with pre-statin LDL-C 190 mg/dL to 29.3% of those with history of CHD (Supplemental Table 4). A post-statin non-HDL-C <100 mg/dL was achieved by 41.5% of patients, ranging from 10.4% of those with a pre-statin LDL-C 190 mg/dL to 63.4% of those with history of CHD.

### Sensitivity analyses to address persistence

In sensitivity analyses among 258 patients who had an LDL-C measurement and 280 patients who had a non-HDL-C measurement one to three months after statin initiation, similarly low percentages of patients achieved 30% and 50% reductions in LDL-C and non-HDL-C as were seen in the primary analyses using lipid measures closest to 12 months post-statin initiation (Supplemental Table 6 for LDL-C and Supplemental Table 7 for non-HDL-C).

## DISCUSSION

Among a geographically diverse population of PLWH in the US, the mean reduction in LDL-C after initiating statins was lower than anticipated. Only one-third of patients had an LDL-C reduction 30% and less than 10% of patients had an LDL-C reduction 50%. The proportions of patients achieving 30% and 50% reductions in non-HDL-C was similarly low. Less than half of patients achieved a post-statin LDL-C <100 mg/dL or a non-HDL-C <130 mg/dL. Overall, less than 10% of patients initiated a high-intensity statin.

A potential contributor to the small LDL-C reduction is the low percentage of patients initiating treatment with a high-intensity statin. Due to pharmacokinetic interactions, HIV treatment guidelines recommend starting atorvastatin or rosuvastatin at a moderate-intensity dose and titrating carefully while monitoring for myopathy when used in patients taking ARV regimens containing some ritonavir-boosted PIs or cobicistat.<sup>4</sup> High-intensity dosing of atorvastatin (> 20 mg) is contraindicated in patients taking ritonavir-boosted darunavir, cobicistat-boosted darunavir, or ritonavir-boosted lopinavir, and use of atorvastatin at any dose is contraindicated in patients taking cobicistat-boosted atazanavir or ritonavir-boosted tipranavir.<sup>4</sup> High-intensity dosing of rosuvastatin (> 10mg) is contraindicated in patients taking ritonavir-boosted atazanavir, cobicistat-boosted atazanavir, or ritonavir-boosted lopinavir.<sup>4</sup> In the current study, half of the patients initiated on statins were taking PIs or cobicistat. In addition, HIV providers may be less likely to prescribe high-intensity statins in general, even among patients for whom they are not contraindicated, due to a high awareness of the risk for drug-drug interactions between some ARVs and statins. A number of patients were taking fibrates at baseline and the potential for drug-drug interactions between fibrates and statins resulting in increased risk for myopathy may have caused providers to favor using a lower intensity statin.<sup>17</sup> However, the major concern for drug-drug interactions is between statins and gemfibrozil in particular, which few patients were taking.

One-third of the patients in the current study were initiated on pravastatin, likely due in part to its favorable safety profile in patients taking PIs.<sup>2, 4</sup> In addition, cost or insurance formularies may have contributed to pravastatin use given our study period of 2009 through 2013. Pravastatin was available as a generic medication in 2006,

whereas generic atorvastatin and rosuvastatin did not become available until 2011 and 2016, respectively.<sup>18, 19</sup> However, rosuvastatin is more effective in reducing LDL-C than pravastatin in PLWH, even when taken at a moderate-intensity dosage.<sup>20–22</sup> In addition, a large study on the comparative effectiveness of statins in PLWH at two CNICS sites reported that atorvastatin and rosuvastatin more effectively reduced LDL-C than pravastatin at equivalent doses.<sup>23</sup> The National Lipid Association recommends using atorvastatin, rosuvastatin, or pitavastatin, the latter of which has no significant interactions with ARVs, as the preferred agents for treatment of dyslipidemia in PLWH.<sup>2</sup>

During most of our study period the ATP III guideline was being used to guide statin therapy in the US, which focuses on LDL-C and non-HDL-C targets rather than statin intensity.<sup>11</sup> This may be another contributor to low use of high intensity statin for initial therapy. Whether deficits in HIV provider awareness of cholesterol management guidelines play a role in the low use of high-intensity statins is unclear. A number of studies have demonstrated deficits in the management of CVD risk factors among PLWH, but there is a paucity of data on HIV provider awareness of guidelines.<sup>24</sup> In addition, it is possible that even providers who are well aware of guidelines place lower priority on lipid management in their focus on HIV-related care.

Based on meta-analyses of general population studies, a mean LDL-C reduction of 30% to <50% is anticipated with a moderate-intensity statin and 50% with a high-intensity statin.<sup>1</sup> The mean reduction in LDL-C in the current study was substantially smaller. Low adherence to statins is common among uninfected persons and may have contributed to the small LDL-C reduction present in the current study.<sup>25, 26</sup> In addition, a substantial number of patients started on statin therapy do not persist in taking them long-term.<sup>27, 28</sup> In the current study population, nearly 25% of patients initiating statins in CNICS and with available lipid measures discontinued treatment prior to the LDL-C measurement closest to 12 months post-statin initiation. We excluded these 225 patients from the current analyses on LDL-C response. However, it is possible that some of the CNICS patients still prescribed a statin at the time of their post-statin LDL-C measurement and included in the analyses were no longer taking it. For this reason, we performed sensitivity analyses restricted to patients with an LDL-C available one to three months after statin initiation. A similarly low percentage of these patients achieved LDL-C reductions 30% and 50% when compared with our primary analyses. Therefore, it seems unlikely that poor persistence played a large role in our findings.

Small clinical trials of moderate-intensity statins in PLWH have reported mean reductions in LDL-C of 20–25%.<sup>29–32</sup> While these reductions are higher than observed in the current study, they are still lower than the 30% reduction anticipated based on meta-analyses of general population studies.<sup>1</sup> The median reduction in LDL-C after 12 weeks was 50% in one small clinical trial of atorvastatin 80mg versus placebo among PLWH.<sup>33</sup> However, more randomized trials are needed on LDL-C response to different statins among PLWH. An important question is whether PLWH may be less responsive to statin therapy than uninfected persons. If so, a number of factors could potentially contribute to this difference, including the metabolic effects of ARVs, lower baseline LDL-C levels, differences in lifestyle factors such as diet and physical activity, or higher levels of chronic stress.<sup>4, 34–36</sup>

There are no clinical trials and only a few observational studies comparing response to statins between PLWH and uninfected persons.<sup>5, 6, 8, 37</sup> A large cohort study by Silverberg et al. found that PLWH experienced a lower reduction in LDL-C than uninfected individuals after adjustment including baseline LDL-C and dose-equivalents of individual statins, but the difference was small (25.6% versus 28.3%).<sup>8</sup> PLWH had similar adherence rates to statins as uninfected individuals and were less likely to discontinue treatment. Consistent with the results from the current study, no association was present between use of PIs and LDL-C response, perhaps due to some PIs increasing both statin and LDL-C levels. The role of other variables that could potentially differ between PLWH and uninfected individuals and impact LDL-C response to statins, such as diet, physical activity, and chronic stress, remains unstudied.

Unanticipated findings in the current study were that mean percent change in LDL-C was similar between patients taking moderate- and high-intensity statins and a lack of association between statin intensity and achieving a 30% reduction in LDL-C after multivariable adjustment. The current study may have been underpowered to detect modest differences due to the low number of patients initiated on high-intensity statins. However, another potential contributor to these findings is that patients taking high-intensity statins are more likely to experience side effects and discontinue treatment, or to be less adherent than patients taking moderate-intensity statins, although these differences may be modest.<sup>38, 39</sup>

The indication for statin initiation was unknown for 39% of patients. As much of the current study period took place during the era of ATP III, some of these patients may have had one or more risk factors for CHD as defined by ATP III (hypertension, low HDL-C, smoking, family history of CHD, or older age).<sup>11</sup> The mean pre-statin LDL-C was 134.5 mg/dL and non-HDL-C was 170.3 mg/dL in this group, suggesting many of these patients may have been placed on statins to achieve ATP III lipid targets. These findings indicate a substantial proportion of PLWH initiating statins do not have CHD or diabetes, and may be at low to moderate risk for ASCVD using the Pooled Cohort risk equations. It is unclear whether these patients should continue on a statin as data are lacking on the risk versus benefit of statins in PLWH with low to moderate estimated ASCVD risk. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) aims to provide more insight into the role for statin therapy in such patients.<sup>40</sup> PLWH with low to moderate risk of CVD are being randomized to pitavastatin 4mg daily or placebo and will be followed for a mean of 72 months to assess for incident CVD events.

There is a lag in the completeness of CNICS data such that we were unable to include data from 2014 and 2015 in our analyses. Thus we are unable to know whether there have been substantial changes in statin management among HIV-infected patients in CNICS based on the 2013 ACC/AHA cholesterol treatment guideline. From 2009 to 2013 there was an upward trend use of high-intensity statins as initial therapy, however the change was small. In addition, to address the fact that most of the study period occurred under the ATP III guideline which focuses on LDL-C targets, we conducted an analysis of the percentage of patients achieving an LDL-C <70 and <100 mg/dL. Patients fared better in terms of achieving an LDL-C target of <100 mg/dL than achieving a 30% reduction in LDL-C. However, we note that it was still less than half of patients who met this target.

Hypertriglyceridemia is the most common lipid abnormality among PLWH.<sup>2</sup> Therefore, non-HDL-C may better captures the concentration of atherogenic cholesterol-containing particles in this population than LDL-C.<sup>41</sup> As with LDL-C, a low proportion of patients in the current study achieved a non-HDL-C reduction 30%, highlighting a potential area of residual risk for ASCVD in this population even after treatment with statins.

The current study has several strengths including a relatively large population PLWH initiating statins, geographic diversity, and the ability to control for a number of factors which may influence LDL-C and non-HDL-C response to statins. The current study has known and potential limitations. Due to the retrospective cohort study design, we can observe associations but cannot determine causality. Data on diagnoses and medications in CNICS are obtained from each site's EHR and are subject to entry errors on the part of clinicians. There are likely unmeasured confounders for which we have not accounted including adherence to statins and lifestyle factors such as diet and physical activity. Titration of statin dose was not captured at each CNICS site and we could only evaluate initial statin intensity. Fasting status was not known for the majority of lipid measurements. However, prior studies demonstrate that the effect of non-fasting status on LDL-C levels is not clinically significant.<sup>42</sup> MIs were unavailable for one of the CNICS sites, and information on cerebrovascular or peripheral vascular diagnoses was not available. However, we expect the number of patients who were misclassified in statin indication is small, given the relatively young age of the population and low prevalence of clinical ASCVD.

## Conclusions:

The current study highlights the small reductions in LDL-C and non-HDL-C after statin initiation among PLWH in routine clinical care, which may leave them with an unmet need for ASCVD risk reduction. These findings emphasize the importance of monitoring LDL-C and non-HDL-C response to statin therapy among PLWH. Also, if there is an inadequate response and a change is not contraindicated by drug interactions, increasing statin dosage or changing to a more potent statin may be warranted in order to more fully realize the ASCVD risk reduction benefit of statins in PLWH. However, PLWH should also be evaluated for other factors potentially influencing LDL-C response including adherence, persistence, diet, and physical activity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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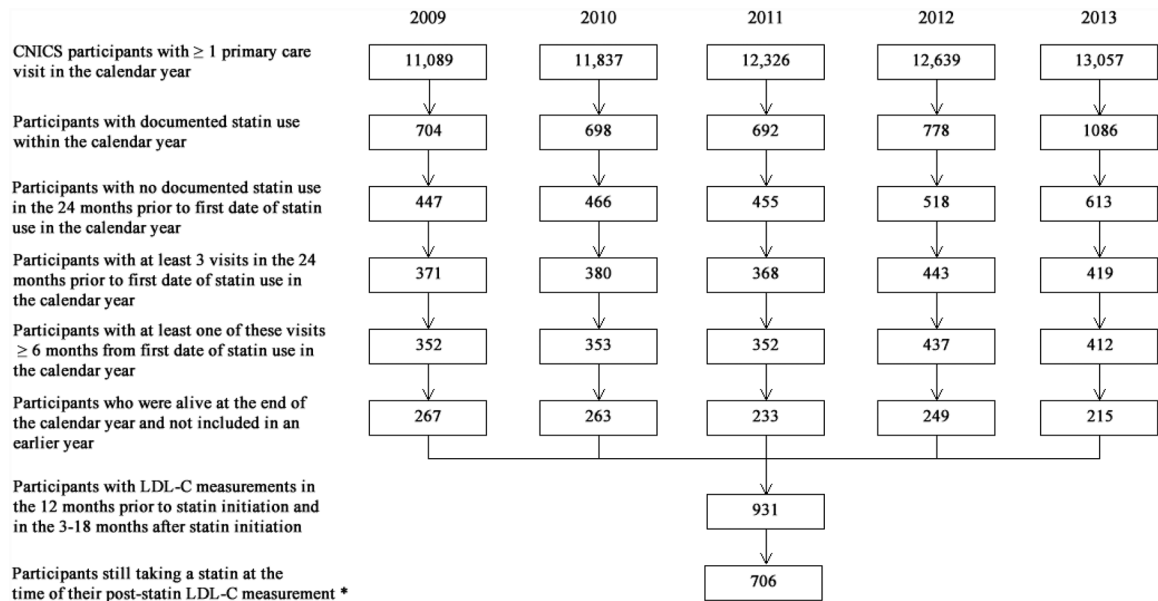
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**Figure 1:**  
Patients included in the current analysis

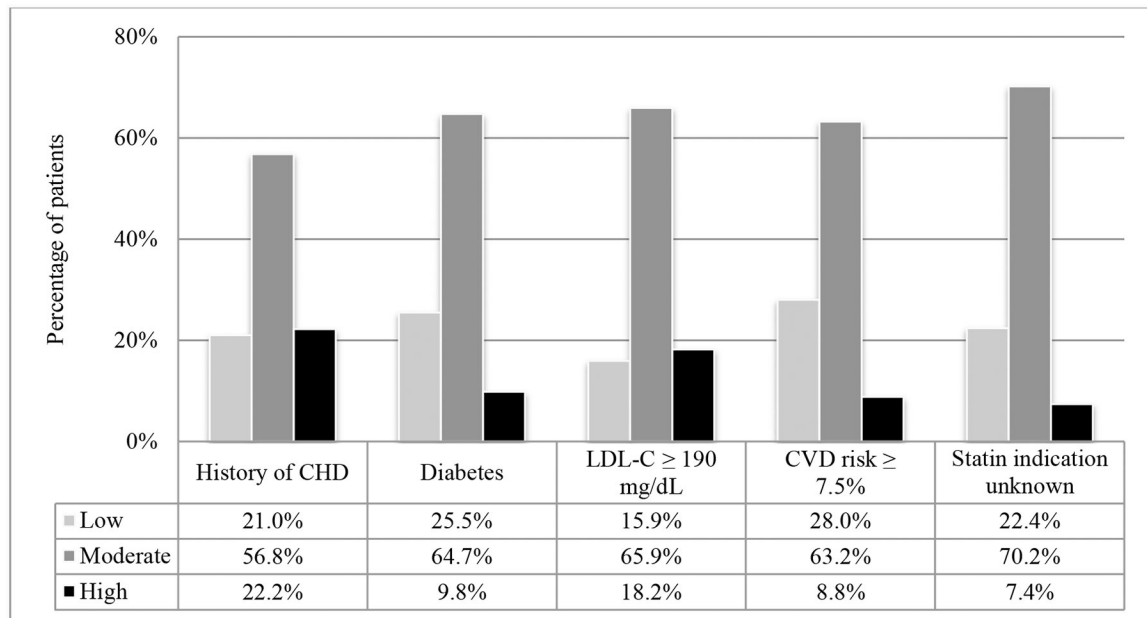
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**Figure 2:**  
 Percentage of patients in the Centers for AIDS Research Network of Integrated Clinical Systems initiating statins who received high-, moderate-, and low-intensity statins  
 Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol

Characteristics of 706 HIV-infected patients initiating statins in the Centers for AIDS Research Network of Integrated Clinical Systems 2009–2013 and still taking a statin at the time of post-statin LDL-C measurement closest to 12 months, stratified by indication for statin use.

Table 1.

Characteristic	Overall (N=706)	History of CHD (N=41)	Diabetes (n=96)	LDL-C 190 mg/dL (n=44)	ASCVD risk 7.5% (n=250)	Statin indication unknown (n=275)
Age, years	50.1 (8.3)	51.9 (7.6)	51.7 (8.5)	46.5 (7.8)	53.9 (7.6)	46.5 (7.1)
Male	84.3	85.4	74.0	84.1	89.7	82.8
Race/ethnicity <sup>a</sup>						
White	53.3	68.3	34.4	61.4	51.1	58.3
African-American	33.7	29.3	51.0	31.8	37.3	25.4
Hispanic	9.3	0	11.5	6.8	8.2	11.5
BMI, (kg/m <sup>2</sup> ) <sup>a</sup>						
Normal (18.5–24.9)	32.8	52.7	20.4	25.0	37.4	31.2
Overweight (25–29.9)	36.1	27.8	36.5	29.5	33.7	40.4
Obese ( ≥ 30)	30.1	14.9	42.7	45.5	28.1	27.3
eGFR, mL/min/1.73m <sup>2</sup>						
60	89.6	70.7	85.4	90.9	89.4	93.9
30–59	8.5	12.2	12.5	9.1	10.4	4.8
< 30	1.8	17.1	2.1	0	0.5	1.2
On PI or cobicistat	50.4	63.4	52.1	50.0	50.8	47.7
CD4 count < 200 cells/μL	7.4	12.2	10.4	9.1	6.8	5.8
Plasma HIV-1 RNA < 200 copies/mL	90.4	80.5	91.7	84.1	89.5	93.2
Chronic Hepatitis C	12.2	24.4	9.4	13.6	17.2	6.5
Hypertension	46.9	70.7	59.4	40.9	55.1	32.5
Current smoking	39.0	54.4	37.7	30.2	53.7	25.1
First statin intensity						
High	9.8	22.2	9.8	18.2	8.8	7.4
Moderate	65.9	56.8	64.7	65.9	63.2	70.2
Low	24.3	21.0	25.5	15.9	28.0	22.4
Non-statin lipid-lowering therapy <sup>b</sup>	23.7	31.7	31.3	18.2	23.6	20.7

Characteristic	Overall (N=706)	History of CHD (N=41)	Diabetes (n=96)	LDL-C (n=44)	ASCVD risk (n=250)	7.5% (n=275)	Statin indication unknown (n=275)
Bile acid sequestrant	0.1	2.4	0	0	0	0	0
Cholesterol absorption inhibitor	2.1	2.4	3.1	0	2.0	2.2	2.2
Fibrate	15.2	26.8	22.9	6.8	13.7	13.4	13.4
Nicotinic acid	3.8	0	5.2	2.3	5.6	2.5	2.5
Fish oil	9.6	12.2	11.5	9.1	8.8	9.4	9.4
Statin type							
Atorvastatin	39.7	24.4	43.8	38.6	37.6	42.6	42.6
Fluvastatin	0.1	0	0	0	0.4	0	0
Lovastatin	0.4	0	0	0	0.4	0.8	0.8
Pravastatin	36.0	41.5	32.3	34.1	41.3	31.9	31.9
Rosuvastatin	19.8	26.8	20.8	25.0	16.8	20.3	20.3
Simvastatin	4.0	7.3	3.1	2.3	3.6	4.4	4.4

<sup>a</sup>Other racial/ethnic groups composed 3.6% of population; 1.2% of patients were underweight

<sup>b</sup>Use of non-statin lipid lowering therapy was measured only at baseline (date of statin initiation)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; LDL-C, low density lipoprotein cholesterol; PI, protease inhibitor

**Table 2:**

Absolute and percent LDL-C reduction among 706 HIV-positive patients in the Centers for AIDS Research Network of Integrated Clinical Systems initiating statins, 2009–2013, stratified by statin indication

Characteristic	Overall	History of CHD	Diabetes	LDL-C	190 mg/dL	ASCVD risk	7.5%	Statin indication unknown
Pre-statin LDL-C, mg/dL, mean (SD)	134.4 (40)	102 (31.6)	115.6 (34.1)	215.1 (25.0)	132.6 (34)	132.6 (34)		134.5 (33)
Post-statin LDL-C, mg/dL, mean (SD)	106.2 (35.1)	81.8 (31.4)	94.1 (28.8)	146.9 (42.6)	104.5 (32.1)	104.5 (32.1)		109.1 (33.2)
Absolute reduction in LDL-C, mg/dL, mean (SD)	-28.2 (36.6)	-20.1 (39.2)	-21.5 (30.3)	-68.2 (45.0)	-28.1 (32.8)	-28.1 (32.8)		-25.5 (36.3)
Percent reduction in LDL-C, mg/dL, mean (SD)	-17.3 (28.0)	-14.1 (39.4)	-15.6 (24.0)	-31.3 (20.1)	-18.2 (26.9)	-18.2 (26.9)		-15.4 (28.7)
Percentage achieving 30% reduction in LDL-C	34.4	31.7	25.0	59.1	33.9	33.9		34.6
Percentage achieving 50% reduction in LDL-C	7.1	17.1	6.3	20.5	6.4	6.4		4.4
Percentage achieving LDL-C <70 mg/dL	12.6	34.1	18.8	0	12.4	12.4		9.5
Percentage achieving LDL-C <100 mg/dL	45.6	73.2	58.3	58.3	11.4	11.4		42.7

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HIV, human immunodeficiency virus; LDL-C, low density lipoprotein cholesterol; SD, standard deviation

**Table 3:**

Characteristics associated with 30% reduction in LDL-C following statin initiation among 706 patients in the Centers for AIDS Research Network of Integrated Clinical Systems initiating statins 2009–2013

Characteristic	Prevalence ratio (95% CI)	
	Univariate	Multivariable adjusted
Indication for statin		
Statin indication unknown	1 (ref)	1 (ref)
History of CHD	0.92 (0.57 – 1.47)	0.94 (0.56 – 1.57)
Diabetes	0.72 (0.49 – 1.06)	0.77 (0.52 – 1.14)
LDL-C < 190 mg/dL	1.71 (1.28 – 2.28)	1.81 (1.34 – 2.45)
ASCVD risk < 7.5%	0.98 (0.79 – 1.22)	1.10 (0.82 – 1.49)
Age, years		
< 40	1 (ref)	1 (ref)
40–49	1.40 (0.91 – 2.15)	1.48 (0.95 – 2.31)
50–59	1.13 (0.73 – 1.75)	1.24 (0.78 – 1.98)
60	1.21 (0.74 – 1.99)	1.35 (0.78 – 2.34)
Male	1.07 (0.80 – 1.43)	0.87 (0.63 – 1.19)
Race/ethnicity		
White	1 (ref)	1 (ref)
African-American	0.71 (0.55 – 0.90)	0.62 (0.48 – 0.81)
Hispanic	1.00 (0.71 – 1.39)	0.92 (0.64 – 1.31)
BMI, (kg/m <sup>2</sup> ) <sup>a</sup>		
Normal (18.5–24.9)	1 (ref)	1 (ref)
Overweight (25–29.9)	1.39 (1.07 – 1.80)	1.39 (1.07 – 1.81)
Obese (≥ 30)	1.11 (0.83 – 1.49)	1.08 (0.81 – 1.46)
eGFR, mL/min/1.73m <sup>2</sup>		
60	1 (ref)	1 (ref)
30–59	0.81 (0.54 – 1.23)	0.90 (0.59 – 1.38)
< 30	1.33 (0.73 – 2.41)	1.99 (1.00 – 3.94)
On PI or cobicistat	0.94 (0.77 – 1.16)	0.92 (0.75 – 1.12)
CD4 count < 200 cells/μL	1.01 (0.68 – 1.48)	1.1 (0.74 – 1.64)
Plasma HIV-1 RNA < 200 copies/mL	0.93 (0.67 – 1.29)	1.01 (0.73 – 1.38)
Chronic Hepatitis C	0.79 (0.55 – 1.13)	0.76 (0.52 – 1.12)
Hypertension	0.94 (0.76 – 1.15)	1.10 (0.88 – 1.39)
Current smoking	0.99 (0.79 – 1.24)	1.02 (0.80 – 1.30)
Statin intensity upon initiation		
High	1 (ref)	1 (ref)
Moderate	1.03 (0.72 – 1.47)	1.05 (0.74 – 1.49)
Low	0.79 (0.52 – 1.19)	0.90 (0.60 – 1.36)
Non-statin lipid-lowering <sup>a</sup> therapy	0.97 (0.76 – 1.23)	1.01 (0.78 – 1.31)

<sup>a</sup>Use of non-statin lipid lowering therapy was measured only at baseline (date of statin initiation)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; LDL-C, low density lipoprotein cholesterol

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