

## Perspective

# Management of Lipid Levels and Cardiovascular Disease in HIV-Infected Individuals: Just Give Them a Statin?

*Current guidelines for managing cholesterol to reduce cardiovascular disease (CVD) risk focus on providing the appropriate intensity of statin therapy to reduce low-density lipoprotein cholesterol (LDL-C) level. There is very little evidence supporting the use of treatments aimed at raising high-density lipoprotein cholesterol level or reducing triglyceride levels. HIV-infected persons have excess risk of CVD compared with the general population. Statins are less effective at reducing LDL-C levels in HIV-infected persons who are also at greater risk for adverse effects from statin treatment. When selecting a statin to achieve desired lowering of LDL-C level, the potential for drug interactions with antiretroviral therapy must be considered. Information from ongoing research is expected to help identify optimal strategies for use of statin treatment in this population. This article summarizes a presentation by James H. Stein, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Chicago, Illinois, in May 2015.*

**Keywords:** HIV, cardiovascular disease, lipids, statins, LDL cholesterol, low-density lipoprotein cholesterol, statin intensity, REPRIEVE trial

## Current Guidelines From the American College of Cardiology and the American Heart Association

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released guidelines for the treatment of blood cholesterol to reduce the risk of atherosclerotic cardiovascular disease (ASCVD).<sup>1</sup> These guidelines differ from previous versions in several respects: 1) they are heavily evidence based, relying almost exclusively on data from randomized clinical trials; 2) their focus is on reduction of low-density lipoprotein cholesterol (LDL-C) with therapy guided by ASCVD risk plus statin dose intensity; 3) treatment is not based on LDL-C level, and there are no LDL-C targets; 4) there are new ASCVD risk-assessment tools that provide better risk estimates for women and minority populations than previous versions; 5) and the new ASCVD risk calculator determines what dose of a statin an individual should be taking.

There is considerable evidence that statin therapy reduces adverse cardiovascular disease outcomes. A meta-analysis reported by the Cholesterol Treatment Trialists' Collaboration in 2010 included 129,526 participants in statin or control trials and 39,612 participants in 5 trials of more intensive or

less intensive statin therapy.<sup>2</sup> Median follow-up was 5.1 years. In the meta-analysis, each 39 mg/dL reduction in LDL-C level was associated with a 10% reduction in all-cause mortality, a 20% reduction in coronary-related mortality, and a 20% reduction in major ASCVD-related events, including a 26% reduction in death caused by myocardial infarction (MI) or coronary heart disease, a 24% reduction in percutaneous coronary intervention and coronary artery bypass grafting, and a 15% reduction in incidence of stroke (all  $P < .0001$ ). Benefits of statin therapy were observed in nearly all subgroups, including persons with or without heart disease or diabetes mellitus, men and women, and across age groups.

The ACC/AHA guidelines classify statin doses by 3 levels of intensity based on their ability to lower LDL-C levels in the general population (Table 1): high-intensity doses (atorvastatin 40-80 mg per day or rosuvastatin 20-40 mg) are expected to reduce LDL-C by 50% or more; moderate-intensity doses (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2-4 mg) are expected to reduce LDL-C by 30% to 50%; and low-intensity doses (simvastatin 10 mg, pravastatin 10-20 mg, lovastatin 20 mg, fluvastatin 20-40 mg, or pitavastatin 1 mg) are expected to reduce LDL-C by 30% or less. Individual LDL-C responses to statin therapy are expected to vary in clinical practice. Simvastatin 80 mg is not recommended for use, owing to increased risk of myopathy and rhabdomyolysis.<sup>1</sup> Some clinicians avoid high-intensity doses of statins, particularly for individuals who might be at higher risk for developing muscle problems, and may instead choose lower-intensity doses of statins in

**Table 1.** Recommended Statin Doses for Achieving Desired Intensity of Treatment<sup>a</sup>

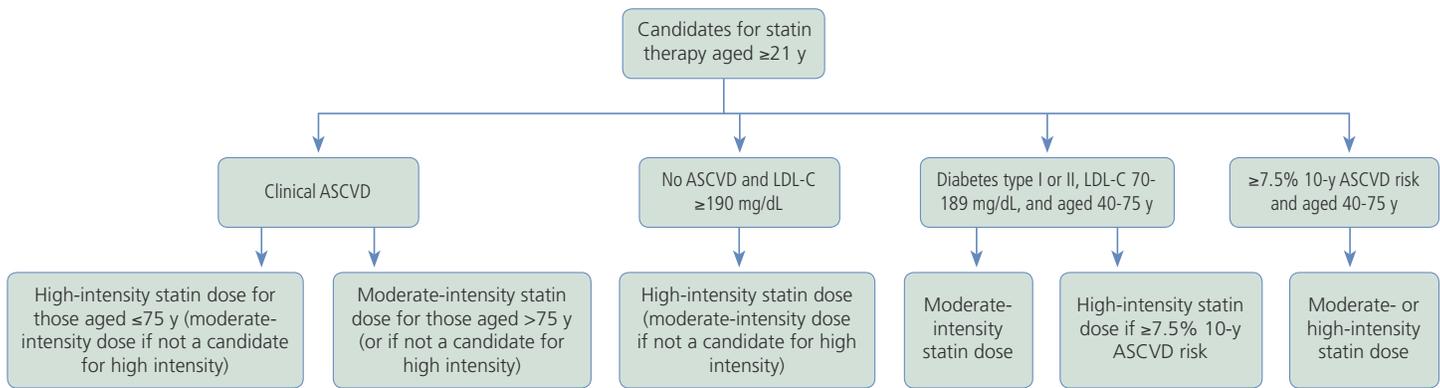
	<b>High Intensity</b> (≥50% decrease in LDL-C)	<b>Moderate Intensity</b> (30%-50% decrease in LDL-C)	<b>Low Intensity</b> (≤30% decrease in LDL-C)
Daily dose	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 2-4 mg	Simvastatin <sup>b</sup> 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Abbreviations: LDL-C, low-density lipoprotein cholesterol. Adapted from Stone et al.<sup>1</sup>

<sup>a</sup>Individual responses to statin therapy varied in randomized controlled trials and are expected to vary in clinical practice.

<sup>b</sup>Simvastatin 80 mg is not recommended by the US Food and Drug Administration owing to the risk of myopathy and rhabdomyolysis.

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**Figure.** Individuals who may benefit from statin therapy and the recommended intensity of their treatment, by group. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. Adapted from Stone et al.<sup>1</sup>

conjunction with nonstatin interventions that have less evidence of reduction of cardiovascular events but also have less risk of causing muscle problems (eg, ezetimibe or bile acid-binding resins) (see Table 2 for recommended statin doses and their intensities in individuals taking antiretroviral therapy).

The Figure shows 4 groups of individuals who may benefit from statin therapy and the recommended intensity of their treatment: 1) individuals with clinical ASCVD, including acute coronary syndrome, MI, angina, revascularization, transient ischemic attack, stroke, and peripheral arterial disease; 2) individuals without ASCVD who have LDL-C levels of 190 mg/dL or higher, likely caused by familial hypercholesterolemia; 3) individuals aged 40 years to 75 years with type I or type II diabetes mellitus; and 4) individuals with a 10-year ASCVD risk of 7.5% or higher, calculated using newer risk-assessment tools. Other considerations when deciding about statin therapy include diabetes mellitus in individuals who are younger than 40 years or older than 75 years, a family history of premature ASCVD, an elevated lifetime risk of ASCVD, an LDL-C level of 160 mg/dL or higher, a high-sensitivity C-reactive protein (hs-CRP) level of 2.0 mg/L or higher, and subclinical atherosclerosis indicated by a coronary artery calcium score of 300 or higher or an ankle-brachial index number below 0.9.

### Considerations in HIV Infection

The ACC/AHA guidelines acknowledge areas, including HIV infection, in which there are insufficient data from randomized clinical trials to provide high-level, evidence-based recommendations. Individuals with HIV infection are at increased risk of ASCVD. Most ASCVD risk in HIV-infected persons is attributable to traditional risk factors, including increasing age, male sex, smoking, diabetes mellitus, family history, hypertension, and dyslipidemia. Some excess risk is related to HIV infection, but how well ASCVD risk predictors work in HIV-infected individuals or how the excess risk associated with HIV infection can be captured with risk-assessment tools has not been established.

Perhaps the best data on excess CVD risk in HIV infection comes from the Veterans Aging Study Virtual Cohort.<sup>3</sup> In the study, which included 27,350 HIV-infected persons and 55,109 uninfected persons, higher rates of acute MI per 1000 person-years were observed among HIV-infected persons than uninfected persons aged 40 years to 49 years (2.0/1000 person-years vs 1.5/1000 person-years), 50 years to 59 years (3.9/1000 person-years vs 2.2/1000 person-years), and 60 years to 69 years (5.0/1000 person-years vs 3.3/1000 person-years). On multivariate analysis, the adjusted hazard ratio for MI in HIV-infected persons versus uninfected persons was 1.48 (95% confidence interval, 1.27-1.72). Some practitioners translate this 40% to 50% increased risk into a lower threshold for initiation of statin therapy. For example, a 5% 10-year risk for ASCVD might be used as the threshold for initiating treatment in HIV-infected persons who otherwise have no history of ASCVD, diabetes mellitus, or very high LDL-C levels.

Statins effectively reduce total cholesterol and LDL-C levels in persons with HIV infection, although their efficacy is somewhat reduced compared with the general population. They improve endothelial function and reduce progression of carotid intima-media thickness, although it is unclear whether statins reduce coronary calcium in the context of HIV infection. HIV-infected persons exhibit more frequent adverse effects during statin therapy, including more frequent elevation of creatine kinase and abnormal liver function test results, and are at risk for drug interactions between antiretroviral and lipid-lowering drugs.<sup>4-6</sup> In the absence of sufficient data from clinical trials regarding lipid lowering in HIV-infected persons, Table 2 provides some guidance on the use of high-, moderate-, or low-intensity statin treatment for individuals taking antiretroviral therapy, based on pharmacokinetic data and safety considerations.<sup>1</sup>

The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial will evaluate the effects of pitavastatin 4 mg daily or a placebo in approximately 6500 HIV-infected persons aged 40 years or older who are not candidates for statin therapy based on current guidelines (see also Grinspoon et al<sup>7</sup>). The primary end point is composite major

adverse cardiac events, which include ASCVD-related death, MI, unstable angina, transient ischemic attack, stroke, or arterial revascularization. Secondary end points include individual major adverse cardiac events, overall mortality, LDL-C level, immune function, AIDS-related or non-AIDS-related events unrelated to CVD, and safety. Ascertaining the effects of statin therapy on inflammatory markers and immune activation in the context of HIV infection will be of particular interest in helping to determine if the excess CVD risk and the benefits associated with statin treatment are reflected by such markers.

### Beyond the Guidelines: Do High-Density Lipoprotein Cholesterol and Triglyceride Levels Matter?

The ACC/AHA guidelines do not review evidence for treatment based on low high-density lipoprotein cholesterol (HDL-C) level, high triglyceride level, or combined dyslipidemia. Further, they contain only limited information and recommendations on the use of biomarkers or atherosclerosis imaging, because of a relative paucity of data from clinical trials. Available data indicate that attempts to increase HDL-C levels in persons receiving statin therapy do not result in risk reduction beyond that already achieved with statin therapy.

In the TNT (Treating to New Targets) trial, participants with heart disease had a reduced risk for CVD-related events while taking atorvastatin 80 mg versus atorvastatin 10 mg. In a post hoc analysis reported in 2007, risk for a CVD-related event was inversely associated with HDL-C quintile ( $P = .04$ ); among persons whose LDL-C levels were reduced to below 70 mg/dL while taking statin therapy, HDL-C level was an independent predictor of CVD-related events ( $P = .03$ ).<sup>8</sup> Based on these and other findings, trials of niacin therapy added to statin therapy to raise HDL-C level and to determine if additional preventive benefit could be achieved were conducted. In the AIM-HIGH trial, 3414 participants with ASCVD who had LDL-C levels of 180 mg/dL or lower, triglyceride levels of 150 mg/dL to 400 mg/dL, and HDL-C levels of 40 mg/dL or lower in men and 50 mg/dL or lower in women received statin therapy and were randomly assigned to receive extended-release niacin or a placebo. After 4 years of follow-up, there was no difference in CVD-related events between the 2 groups ( $P = .79$ ).<sup>9</sup>

In the larger HPS2-THRIVE trial, 25,673 patients with ASCVD had higher HDL-C levels and lower triglyceride levels when niacin and laropiprant (a drug that prevents niacin-related flushing) were added to statin treatment, although there was no significant difference in prevalence of CVD-related events over 4 years ( $P = .29$ ).<sup>10</sup> Niacin treatment was associated with an absolute 3.7% increase in incidence of serious adverse effects, including diabetes mellitus, infection, gastrointestinal effects, and myalgia; the relative risk for such effects was 5.2 among persons in China compared with 1.5 among persons in Europe.

In the absence of demonstrated reductions in ASCVD risk associated with pharmacologically induced increases in HDL-C levels in persons taking statins, it is worthwhile to

**Table 2.** Suggested Doses for Achieving Desired Intensity of Statin Treatment in HIV-Infected Individuals Taking Antiretroviral Therapy

High Intensity	Moderate Intensity	Low Intensity
With PI- or cobicistat-based regimens:		
Atorvastatin 20 mg	Atorvastatin 10 mg	Pravastatin 10-20 mg
Rosuvastatin 20 mg	Rosuvastatin 10 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	
With NNRTI-, raltegravir-, or dolutegravir-based regimens:		
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20 mg	Rosuvastatin 10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

Abbreviations: BID, twice daily; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor. Courtesy of Michael P. Dube, MD. Adapted from Stone et al.<sup>1</sup>

consider the activity of HDL-C. It was once believed that HDL was mainly involved in reverse cholesterol transport. However, as atherosclerotic disease appears to have emerged as a dominant cause of death only in the last approximately 150 years, it is unlikely that HDL-C evolved solely to transport excess cholesterol back to the liver. Indeed, HDL-C also acts as an antiinflammatory particle with powerful antioxidant effects that is involved in host defense and immunity. Published data indicate a role for HDL in protection from endotoxins and trypanosomiasis. Data from Mendelian randomization studies do not strongly support the role of HDL-C in protecting against ASCVD. It appears that HDL-C is a marker rather than a mediator of disease and is not a suitable target of treatment.<sup>11,12</sup>

Triglyceride levels have been a controversial CVD risk factor because they are associated with other risk factors such as obesity, diabetes mellitus, adverse lifestyle habits, inflammation, low HDL-C levels, small LDL particles, and excess LDL particles. However, Mendelian randomization studies have indicated that triglycerides play a potential causal role in ASCVD, albeit not as strong a role as LDL-C.<sup>12-14</sup> Nevertheless, there is little evidence to suggest that adding triglyceride-lowering medications to statin therapy provides additional risk reduction.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study evaluated the addition of fenofibrate or placebo to simvastatin in more than 5000 participants with diabetes mellitus, an average triglyceride level of 162 mg/dL, an average HDL-C level of 38 mg/dL, and an average LDL-C level of 100 mg/dL. After up to 7 years of follow-up, there were no differences between the fenofibrate group and the placebo group with regard to the composite end point of ASCVD-related death, nonfatal MI, or nonfatal stroke, a combined

end point of revascularization and congestive heart failure, or death from any cause.<sup>15</sup> Subgroup analysis suggested a possible benefit of fibrate therapy in reducing the risk of ASCVD-related outcomes in individuals with triglyceride levels above 204 mg/dL and HDL-C levels below 34 mg/dL ( $P = .06$ ). A similar potential benefit was observed with niacin in a subgroup of the AIM-HIGH study who had high triglyceride levels ( $\geq 198$  mg/dL) and low HDL-C levels ( $< 33$  mg/dL;  $P = .07$ ).<sup>16</sup> Thus, fibrates or niacin may add some benefit to statin treatment in individuals with high triglyceride levels and low HDL-C levels, although these treatments are associated with adverse effects.

Fish oil has been used to lower triglyceride levels, but there is little evidence that it is of benefit when added to statin therapy. The benefit of an eicosapentaenoic acid (EPA) formulation was shown in a Japanese study reported in 2007 in which the addition of EPA to pravastatin or simvastatin was assessed in more than 18,000 participants whose total cholesterol level was above 253 mg/dL; average baseline LDL-C level was 183 mg/dL, average HDL-C level was 59 mg/dL, and average triglyceride level was 154 mg/dL. In the context of a 25% reduction in LDL-C level in both groups and a 9% and 4% reduction ( $P < .001$ ) in LDL-C level in the groups taking EPA or statins only, respectively, there was a significant absolute reduction of 0.7% ( $P = .011$ ) in risk of major coronary events among all individuals taking EPA. Risk reduction was significant in secondary prevention (absolute reduction of 2%;  $P = .048$ ) but not in primary prevention.<sup>17</sup>

### Use of Nonstatin Drugs

In individuals with triglyceride levels above 500 mg/dL, fibrates (or niacin or fish oil) should be added to statin treatment to reduce the risk of pancreatitis. In all individuals receiving statin therapy, the addition of nonstatin treatments can be considered in cases of statin intolerance or persistent suboptimal response to statin treatment (eg,  $< 50\%$  decrease in LDL-C level, LDL-C level remaining  $> 100$  mg/dL in those receiving high-intensity treatment, or  $< 30\%$  decrease in LDL-C level in those receiving moderate-intensity treatment). Ezetimibe is a likely choice for nonstatin treatment in such cases, as it has been shown to reduce the risk of CVD-related events.

In the IMPROVE-IT trial conducted in more than 18,000 persons diagnosed with acute coronary syndrome within 10 days of entry into the study, the addition of ezetimibe to simvastatin 40 mg resulted in a 10% reduction ( $P = .003$ ) in risk for the composite end point of CVD-related death, MI, or stroke over 7 years.<sup>18</sup> The rate of ASCVD events in the group that received simvastatin alone was 22.2% in the context of an achieved LDL-C level of 70 mg/dL; the rate of ASCVD events in the group that received ezetimibe and simvastatin was 20.4% in the context of an achieved LDL-C level of 53 mg/dL. The number needed to treat with ezetimibe to prevent 1 additional adverse event was 56. The correlation between a reduction in ASCVD events and a reduction in LDL-C level in the trial was consistent with that observed in other

lipid-lowering trials,<sup>19</sup> indicating that preventive benefit is largely caused by a lowering of LDL-C level. Although statins have antiinflammatory properties and some immunomodulatory effects, treatment should be directed at lipid lowering.

### Summary

Reduction of CVD risk through lipid lowering is guided by determination of the appropriate dose intensity of statin treatment. Nonstatin therapies are less effective and can be considered additional therapy if statins are not well tolerated or if individuals show persistent suboptimal response to statin therapy. HIV-infected persons are at increased risk for CVD, although statins are less effective for lowering LDL-C level in such persons and are associated with more adverse effects. It is essential to consider potential drug interactions when selecting a statin for patients taking antiretroviral therapy. Information from the REPRIEVE trial will help define optimal approaches to statin treatment in this population. Further, practitioners should remember that smoking is a more powerful predictor of ASCVD risk in individuals with HIV infection. Helping patients to stop smoking and other adverse lifestyle habits may do more to reduce ASCVD risk in patients with HIV infection than titrating doses of lipid medications or combining such medications. 

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