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Overcoming Obstacles in Lipid-lowering Therapy in Patients with HIV - A Systematic Review of Current Evidence

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Abstract

Cardiovascular risk management in human immunodeficiency virus (HIV)-infected individuals is gaining increased attention due to the rising incidence and prevalence of cardiovascular disease in this population. Despite the availability of efficacious treatment strategies, implementation of guideline advocated preventive therapy, such as lipid-lowering therapy with statins, is hampered by perceived, expected, and real side effects as well as by expected interactions with combination antiretroviral therapy. These obstacles to optimal treatment have resulted in a large gap between the number of patients in whom lipid-lowering therapy is indicated and those actually taking lipid-lowering medication. In the past few years, research has shown that the majority of patient-reported side effects is not causally related to statin therapy but is attributable to the nocebo effect. Furthermore, excessive caution due to expected drug interactions between statins and antiretroviral therapy is often unnecessary, especially with novel classes of antiretroviral therapy. The main aim of this review is to discuss the causes and consequences of this lipid-lowering treatment gap in HIV-infected patients together with a practical guide on how to overcome these obstacles. In addition, new treatment options on the optimal cardiovascular management focusing primarily on novel classes of antiretroviral therapy and lipid-lowering medication will be discussed. **(AIDS Rev. 2018;20:205-219).**

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Key words

Human immunodeficiency virus infection. Cardiovascular risk. Statin. Integrase strand transfer inhibitor. Proprotein convertase subtilisin kexin-9 inhibitor.

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Introduction

Since the late 1970s, the rate of cardiovascular disease (CVD) mortality in the general population has halved in most industrialized countries due to the successful treatment of population risk factors such as smoking, hypertension, and cholesterol[1]. This change in the population prevalence of risk factors has strongly increased the vascular disease-free survival in low- and high-risk populations.

Similarly, the use of potent combination antiretroviral therapy (cART) has dramatically improved the outcome in patients infected with the human immunodeficiency virus (HIV) from a deadly disease to chronic morbidity with vastly increased survival[2]. This improvement in HIV specific care gives rise to a situation in which the prevalence of non-AIDS-related comorbidities - such as CVD - among HIV-infected individuals is steadily increasing[3]. Thus, in the HIV-infected population, adequate strategies to prevent CVD are needed, specific to the HIV-infected population, its comorbidities and antiretroviral therapy.

This systematic review summarizes the existing evidence on CVD risk in HIV-infected patients and subsequently discusses the current obstacles in the implementation of adequate risk management strategies with a focus on low-density lipoprotein (LDL) lowering. In addition, the effects of new developments in both antiretroviral (e.g., integrase inhibitors) and lipid-lowering agents (e.g., anti-proprotein convertase subtilisin/kexin 9 [PCSK9]) on the optimal cardiovascular management in these patients will be discussed.

Method

This systematic review was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analysis framework. A systematic literature search using two databases (PubMed Medline and the Cochrane library) was performed using the following search terms: HIV infection OR HIV; statin OR hydroxymethylglutaryl-coa-reductase inhibitors; intolerance OR side effects OR myalgia OR muscle associated symptoms; adherence. We included only articles written in English. Exclusion criteria for the studies were as follows: (1) article concerns non-HIV-infected population, (2) article concerns treatment-naïve HIV-infected patients, and (3) article does not address side effects due to use of statin therapy.

Data extraction and validity

After applying the exclusion criteria and removing duplicates, 5 articles were selected, and a further 6 articles were added after cross-checking references of the identified studies (Figure 1). Full text evaluation of the remaining studies for eligibility was performed independently by two authors (JEA and JW) using a standardized data extraction form.

Inconsistencies between study forms were discussed and reviewed by a third author (CD) for majority decision. Variables included in the form were study design, method, and duration of follow-up, number of patients, patient characteristics (i.e., age, sex, ethnicity, and comorbidity), investigated statin, reported adherence, reported toxicity, and number of patients with toxicities. A summary of study characteristics is given in table 1. Results were expressed as changes in lipid-profile and the occurrence of symptoms and/or (laboratory) toxicity due to statin use among HIV-positive patients.

HIV and cardiovascular risk

Compared to treatment-naïve HIV-infected patients and HIV-uninfected patients, those infected with HIV have an increased relative risk of (subclinical) CVD of approximately 1.5 to 2 fold[4], which is due to both HIV-specific risk factors and increased prevalence of classical cardiovascular risk factors. The latter include diabetes mellitus type 2 (DM2), smoking, dyslipidemia, and hypertension[5,6]. Although DM2 is not highly prevalent comorbidity among HIV-infected patients (prevalence of 2.85% among 33.389 HIV-infected patients)[7], DM2 does develop at an earlier age with a higher prevalence among HIV-infected patients when compared to age-matched patients without HIV[8]. DM prevalence is 3.8% higher (confidence interval [CI] 1.8-5.8%) in HIV-infected adults compared with general population adults[8]. Probably even more important is the observation that HIV-positive patients are more likely to smoke (42.4% vs. 20.6%) and are less likely to quit smoking when compared to the general adult population (32.4% vs. 51.7%)[9]. Therefore, smoking remains an important cardiovascular risk factor in patients with HIV and smoking cessation may confer a large reduction in cardiovascular risk. The age HIV cohort study demonstrated that hypertension was also more prevalent among HIV-infected individuals compared to a well-matched HIV-negative control group (45.4% vs. 30.5%)[5]. Finally, HIV-infected patients had

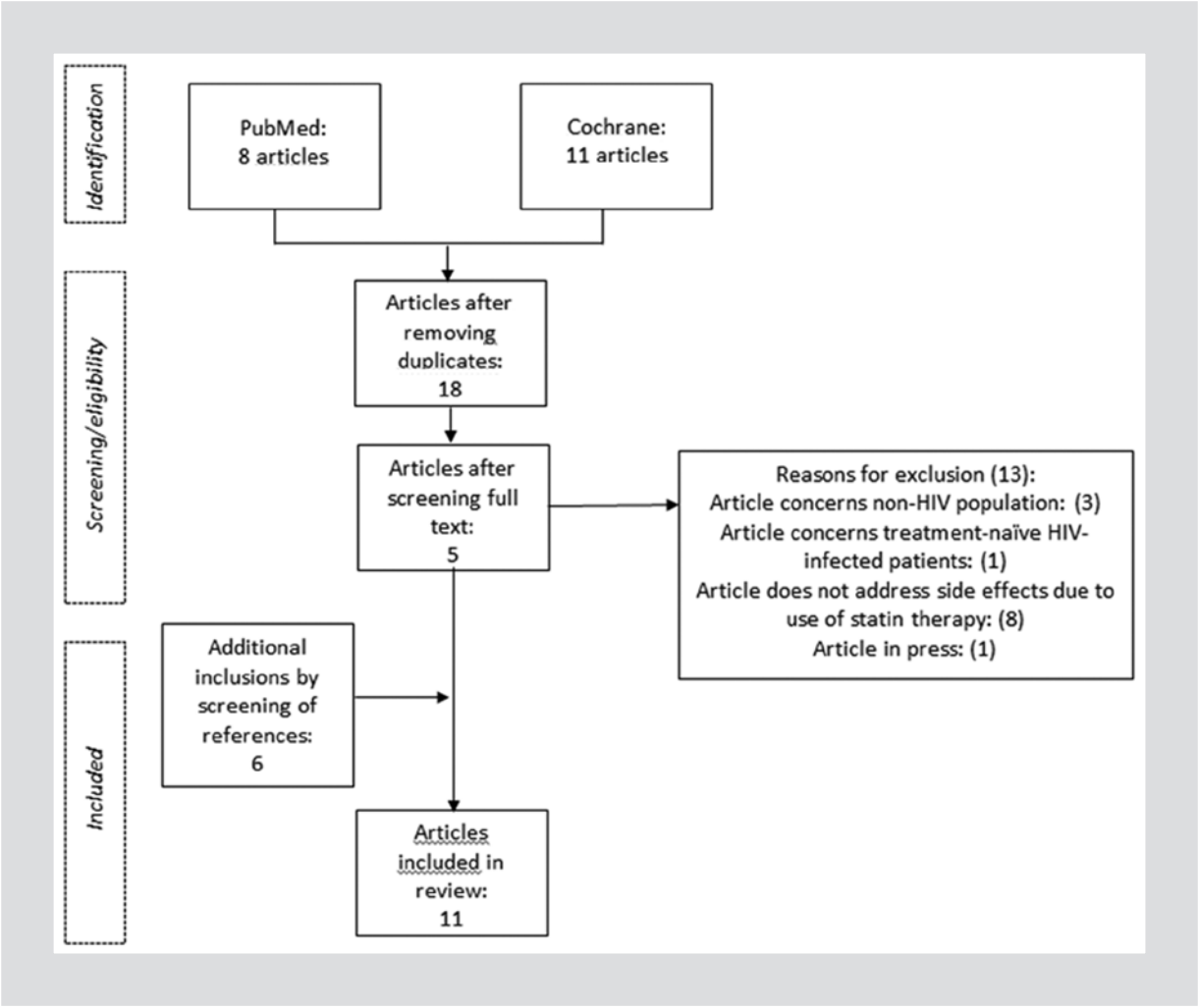


Figure 1. *Process of study selection.*

an increased carotid intima-media thickness, a subclinical marker of CVD, and compared to HIV-uninfected patients[10].

Next, to these classical cardiovascular risk factors, there are also HIV-specific variables that play a role in the development of CVD. Firstly, the HIV promotes a state of low-grade chronic inflammation through initial damage to the gut-associated lymphoid tissue and subsequent leakage of enteric bacterial content into the bloodstream and activation of macrophages[11,12]. Since activated macrophages are a key component of the atherosclerotic process and have been shown to migrate toward the atherosclerotic plaque[13], this constant immunomodulation has been shown to increase the risk of atherosclerosis[14]. Additional mechanisms possibly involved in the development of atherosclerosis include direct virus-induced endothelial dysfunction[15] and CD4 cell count depletion[16]. The balance between endothelial vascular injury and repair is important for the integrity of the endothelium[17]. Endothelial progenitor cells (EPCs) are needed in the bloodstream due to their vascular repair capacity. The study of López et al. showed that certain EPC levels were significantly lower in HIV-infected than in uninfected controls ($p = 0.012$), which supports the interpretation that the protective effect of EPC on the development of atherosclerosis is impaired in HIV infection[17]. The above-mentioned CD4 cell count depletion may be more prevalent in non-Western countries where the changed guidelines that recommend to initiate cART in all patients irrespective of CD4 cell counts have not yet been implemented[18]. Furthermore, some frequent comorbidities have an additive effect on the increased cardiovascular risk seen in HIV-infected patients. For example, around 20% of HIV-positive patients have chronic

Table 1. Baseline characteristics

Author	Investigated statin	Fibrate used	No.	Mean age (range/SD)	% male Male/female	Country/ethnicity	Comorbidity*
Nakanjako et al.	Atorvastatin	No	Active drug first 15 Placebo first 15	41 (40-50) 47 (43-51)	53.3% 33.3%	Uganda/African	Unknown
Saeedi et al.	Rosuvastatin	Yes	Ezetimibe group 23 Rosuvastatin group 20	56.5 (7.4) 57.0 (9.9)	95.6% 85.0%	82.6% caucasian 75.0% caucasian	Diabetes 34,8% Hypertension 56,5% Smoking 26,1% BMI 26.0 (4.2) Diabetes 35.0% Hypertension 30.0% Smoking 5.0% BMI 25.3 (4.7)
Penzak et al.	Pravastatin, lovastatin, simvastatin, atorvastatin	No	26	44 (34-69)	22/26	Unknown	Unknown
Ou et al.	Pravastatin Lovastatin Fluvastatin Simvastatin Atorvastatin	No	CVD+/low dose statin 72 CVD+/high dose statin 72 CVD-/low dose statin 393 CVD-/high dose statin 408	50.1 (13.2) 46.9 (1.2) 41.5 (9.4) 41.3 (9.8)	70.8% 86.1% 92.6% 92.9%	Taiwan	Diabetes 34.72% Hypertension 52.8% Dyslipidemia 47.2% Diabetes 33.3% Hypertension 56.9% Dyslipidemia 47.2% Diabetes 14.2% Hypertension 18.58% Dyslipidemia 45.5% Diabetes 12.0% Hypertension 17.65% Dyslipidemia 48.3%
Stein et al.	Pravastatin	No	20	44.1 (1.6)	90%	White (16), black (3), Asian (1)	Diabetes 1/20 Hypertension 7/20 Smoking 6/20
Singh et al.	Atorvastatin Pravastatin Rosuvastatin Other	No	303 280 95 22	Age>50 17% Age>50 17% Age>50 11% Age>50 18%	88% 83% 89% 82%	White 71%, black 20%, Hispanic 6%, other 3% White 68%, black 26%, Hispanic 11%, other 3% White 71%, black 28%, Hispanic 0%, other 1% White 77%, black 23%, Hispanic 0%, other 0%	Diabetes 13%, BMI>30 21% Diabetes 20%, BMI>30 23% Diabetes 16%, BMI>30 23% Diabetes 27%, BMI>30 18%

(Continues)

Table 1. Baseline characteristics *(Continued)*

Author	Investigated statin	Fibrate used	No.	Mean age (range/SD)	% male Male/female	Country/ethnicity	Comorbidity*
Calza et al.	Rosuvastatin	No	16	44.2 (38-56)	12/4	Unknown	Unknown
Silverberg et al.	Different statin	Yes	Elevated LDL cholesterol level at baseline 616 Elevated TG level at baseline 213	50.5 (9.3) 46.8 (8.8)	90.9% 96.2%	Unknown	Unknown
Milazzo et al.	Atorvastatin, pravastatin, rosuvastatin, simvastatin	No	80	45.5 (42-54)	76.2%	Unknown	Unknown
Aberg et al.	Pravastatin	Yes	174 (86 on statin)	< 25 years 1% 25-34 years 10% 35-44 years 52% 45-54 years 33% Over 55 years 4%	91.0%	White 66%, black 10%, Hispanic 22%, Asian 1%, American Indian 1%	Unknown
Bonnet et al.	Different statins	Yes	245 (66 on statins)	47 (39-58)	76%	Unknown	Unknown

*Diabetes, hypertension, dyslipidemia, smoking, obesity (BMI>25 kg/m2)
BMI: Body mass index, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TG: Triglyceride, CVD: Cardiovascular disease, TC: Total cholesterol. SD: Standard deviation

hepatitis C while it is suggested that coinfection with both HIV and HCV may behave synergistically worsening the CVD risk[19,20]. It is important to point out that several observational studies have reported associations between specific antiretroviral agents and increased CVD risk. For example, the D:A:D study reported on the almost 2 times higher risk associated with abacavir, a nucleoside reverse transcriptase inhibitor, and on cardiovascular events (D:A:D study) compared with patients with no recent use of the drug[21,22]. Subsequent cohort studies together with a meta-analysis and an FDA-report, however, did not confirm this observation[23-25]. In addition, older cART regimens were known to cause hypercholesterolemia, increasing the risk for CVD[26]. However, development of newer cART has led to less effects on cholesterol with a subsequent lower cardiovascular risk.

Lipid-lowering in HIV-infected patients

In the general population, statin therapy is the cornerstone for prevention and treatment of CVD since the use of statins was proven to be very effective in reducing CVD in various patient populations[27]. The lipid-lowering effectiveness of statins in HIV-infected patients on cART was confirmed in a meta-analysis showing significant reductions in plasma total cholesterol (TC) levels, comparable to those in the non-HIV infected population, with similarly low rates of adverse events[28]. Especially, LDL-cholesterol (LDL-C) levels and to a lesser extent triglyceride (TG) levels were both effectively reduced by almost all statins[28]. The studies included in this systematic review confirm that the use of statins is effective among HIV-infected patients. Statins decrease TC levels by 18-27%, TG levels by 15%[29,30] and LDL-C levels by 21%[31]. In addition, research shows that there is a lower CVD risk in HIV-infected patients receiving intensive statin therapy: patients with a high potency statin (i.e., atorvastatin) showed a lower CVD risk compared to patients with a low potency statin (i.e., pravastatin)[32]. These results are outlined in table 2.

CVD guidelines developed for the HIV-positive population

The European AIDS Clinical Society (EACS) states that statins should be used by all HIV-infected patients with established CVD and among those with type 2 diabetes or a 10-year CVD risk of > 10%, irrespective of lipid levels[18]. Lipid treatment goals that are to be used as guidance are adopted from the EACS Guidelines[18] and

are showed in table 3. Although it remains unclear when standard or the optimal treatment goals should be pursued, it is currently recommended that TC levels should be ≤4 mmol/L (155 mg/dL, optimal treatment goal) or 5 mmol/L (190 mg/dL, standard treatment goal) and LDL-C levels should be ≤2 mmol/L (80 mg/dL, optimal treatment goal) or 3 mmol/L (115 mg/dL, standard treatment goal). These recommendations are in contrast to the 2016 ESC guidelines for the general population which clearly defines a risk-based approach with LDL goals of < 2.5 mmol/L (97 mg/dL) and < 1.8 mmol/L (70 mg/dL) dependent on predicted cardiovascular risk[33].

The expected absolute benefit of lipid-lowering depends mainly on the underlying risk of CVD and exposure time of the treatment[18]. Therefore, it is necessary to calculate an individualized CVD risk. Individualized 10-year CVD risk prediction models, such as the atherosclerotic CVD risk score (ASCVD) or the systematic coronary risk evaluation score (SCORE), are used in the general HIV-uninfected population[34]. Using the database from the data collection on Adverse Effects of Anti-HIV Drugs Study (DAD), Friis-Møller et al. developed a cardiovascular risk-assessment model specifically tailored to European HIV-infected patients[35]. It was demonstrated by Krikke et al. that the Framingham Heart Study (FHS) over-estimated overall CVD risk in HIV-infected patients compared to the DAD, ASCVD, and SCORE-NL models[34].

Do we achieve our treatment goals?

The percentage of patients achieving LDL-C levels below threshold levels varies from 23.1% to 52.8%[36-39]. Even though the fact that HIV-positive patients are less likely to achieve target values compared to HIV-uninfected patients[36], they would still benefit from lipid-lowering medication. However, the majority of HIV-positive patients who meet criteria for statin therapy using current guidelines are not receiving it[40]. Despite the high prevalence of dyslipidemia in HIV-infected patients (up to 80%), < 10% of these patients are truly on statins[41]. These low rates of statin prescription may be due to (perceived and expected) side effects or to expected interactions with cART.

Reasons for not achieving our treatment goals

In the general population, approximately 50% of patients discontinue statin therapy within the 1st year of treatment initiation and this percentage increases even further over a longer treatment period[42]. These discontinuations are mostly attributable to non-adherence defined as the extent to which patients are not able to follow the recommendations for prescribed treatments. With statins, non-adherence is mostly due to (perceived and expected) side effects[43].

Side effects

On the one hand, there are real side effects that can be traced back to the pharmacodynamic mechanisms through which statins exert their effects, and on the other hand, there are perceived side effects that are felt by patients but are unrelated to statin use[44]. In either case, it leads to discontinuation of statin use. It is difficult to estimate the true prevalence of statin intolerance since inconsistent definitions are mentioned in literature. In the general population, 10-25%[45,46] of patients receiving statin therapy complain of statin-associated muscle symptoms (SAMS), which is defined by (symmetrical) muscle aches or myalgia, weakness, stiffness, and cramps[47]. However, in an internet survey, up to 60% of statin users reported SAMS[46]. The prevalence of real side effects seems to be between 10 and 15%[48,49], but only very few (< 1%) develop serious side effects such as myopathy, myositis, or rhabdomyolysis[49]. A good definition can help distinguish between perceived and proven statin intolerance. The unified definition of proven statin intolerance is as follows: if after treatment with several statins, at different doses, the muscle symptoms (and/or other mentioned above side effects) are still intolerable and/or abnormal values of biomarkers (> 10-fold increase in CK, together with increases in serum creatinine) remain, and the subject can be characterized as intolerant to statin[50].

The muscle symptoms due to the use of statin therapy in the HIV-infected population that are found in literature are outlined in table 2. In the largest study by Ou et al., none (0.0%) of the 945 examined HIV-infected patients developed muscle symptoms while on statin therapy[32]. This observation was confirmed in other studies in which no significant clinical or laboratory adverse events occurred[51-53]. However, other studies reported on the occurrence of muscle symptoms while using a statin in some HIV-infected patients who did not discontinue statin therapy[29-31,54]. Just like in the general population, inconsistent definitions are used which makes it difficult to estimate the

Table 2. Analysis of outcome and muscle symptoms due to the use of statin therapy

Author	Methodology	Statin therapy	Outcome	Symptoms and/or laboratory toxicities attributed to statin
Nakanjako et al.	12-week randomized double-blind placebo-controlled crossover trial	Atorvastatin 80 mg/day versus placebo	LDL-C and TG reduced significantly among individuals receiving atorvastatin ($p < 0.001$). Mean LDL-C levels were reduced with 21%; from 3.1 mmol/l to 1.0 mmol/L after 12 weeks of therapy	6 patients experienced myalgias. Three were receiving atorvastatin, and three were receiving placebo
Saeedi et al.	12-week prospective, randomized, open-label clinical trial	Ezetimibe 10 mg/rosuvastatin 20 mg ($n = 23$) Rosuvastatin 20 mg ($n = 20$)	Significant between-group differences were observed for mean TC (−1.01 mmol/L vs. −0.50 mmol/L, $p = 0.03$), TG (−0.62 mmol/L vs. −0.17 mmol/L, $p = 0.03$), and non-HDL-C (−0.97 mmol/L vs. −0.53 mmol/L, $p = 0.03$) all in favor of the ezetimibe plus rosuvastatin group	Two patients, both in the rosuvastatin 20 mg group, experienced mild myalgias
Penzak et al.	Retrospective analysis	Pravastatin ($n = 5$), lovastatin ($n = 13$), simvastatin ($n = 10$), atorvastatin ($n = 2$). Different doses	Statins collectively reduced median baseline TC 27% (354-263 mg/dl) and TGs 15% (513-438 mg/dl)	Two patients receiving lovastatin experienced symptoms of myalgia after 2 months of therapy
Ou et al.	Longitudinal cohort study	Different statins in low or high dose	There is a lower CVD risk in HIV patients receiving intensive statin therapy. The high-potency group showed a lower CVD risk compared to that of the low-potency group (HR: 0.42, 95% CI: 0.06-3.13)	0 patients, in both low- and high-dose group, experienced muscle symptoms after 1 year of therapy
Stein et al.	Placebo-controlled, double-blind, crossover study	Pravastatin 40 mg versus placebo	Total and non-HDL-C levels decreased by 18.3% ($p < 0.001$) and 21.7% ($p < 0.001$), respectively	Three patients, all receiving pravastatin, experienced mild myalgia/severe muscle aches
Singh et al.	Retrospective cohort study	Atorvastatin ($n = 303$), pravastatin ($n = 280$), rosuvastatin ($n = 95$), other} ($n = 22$). Different doses	With all statins, mean TC, LDL-C, TG, and non-HDL-C levels were significantly lower than baseline values at periods up to 24 months. HDL-C values did not change significantly over time	15 (2.2% of all study participants) had potentially serious toxicity: an elevation in CPK level (with or without a decline in renal function) was the most common potentially serious toxicity followed by elevations in liver enzymes. Five patients had CPK-level elevations between 1000 and 10,000 U/L (4 on pravastatin and 1 on rosuvastatin) and 1 had an elevation >10,000 U/L (on atorvastatin). 29 (4.3%) had symptomatic toxicity (myalgias/ arthralgias 62%, gastrointestinal symptoms 21%, and fatigue 7%)

(Continues)

Table 2. Analysis of outcome and muscle symptoms due to the use of statin therapy (*Continued*)

Autho	Methodology	Statin therapy	Outcome	Symptoms and/or laboratory toxicities attributed to statin
Calza et al.	Pilot study	Rosuvastatin 10 mg/day	Median reductions in TC and TG versus median baseline values were 21.7% and 30.1%, respectively ($p < 0.01$)	Two out of the 16 treated patients (12%) had mild and transient gastroenteric symptoms. Neither myalgia nor myositis were observed. No significant laboratory adverse events occurred
Silverberg et al.	Retrospective cohort study	Different statins at different doses	Patients with HIV infection had smaller adjusted percentages of decline in LDL-C levels than patients without HIV infection (25.6% vs. 28.3%, $p = 0.001$). HIV-infected patients who used pravastatin had a reduced LDL-C level compared with patients without HIV infection receiving any statin	Rhabdomyolysis was diagnosed in three patients with HIV infection. No clinically recognized cases of myositis or myopathy. Risk for laboratory adverse events was low (< 5%), but it was increased in patients with HIV
Milazzo et al.	Retrospective cohort study	Different statins at different doses	Significant reduction in cholesterol levels ($p = 0.01$)	None of the patients discontinued statins due to liver toxicity or modified their antiretroviral regimen due to drug interaction
Aberg et al.	Randomized, open-label trial	Fenofibrate 200 mg/day ($n = 88$) or pravastatin 40 mg/day ($n = 86$)	Median changes in LDL/HDL/TG were+13/+4/−118 and−30/0/−27 mg/dl in subjects randomized to fenofibrate and pravastatin respectively. All p values were significant except percent change in pravastatin HDL and pravastatin TG. Combination of fenofibrate and pravastatin provides substantial improvements in lipid parameters.	Four subjects (three fenofibrate and one pravastatin) discontinued therapy in the first 12 weeks. Three subjects discontinued therapy between weeks 12 and 28 (two with asymptomatic elevations in lipase and one with thrombocytopenia). No reports of rhabdomyolysis during the 48-week study period
Bonnet et al.	Prospective study	Fibrates ($n = 179$) or statins ($n = 66$)	In the fibrates group, there was a significant mean decrease of TG (−2.29 mmol/L) and TC (−0.55 mmol/L) after 3 months. In the statins group, TC significantly decreased (−0.70 mmol/L) after 12 months	Fibrates and statins were safe; no significant modification of liver enzymes during 12 months of follow-up

LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TG: Triglyceride, CVD: Cardiovascular disease, TC: Total cholesterol

Table 3. Target levels expressed as mmol/L with mg/dL in parenthesis. In case of LDL cannot be calculated due to high TG levels, the non-HDL-C (TC minus HDL-C) target should be used which is 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C target

Target	Optimal	Standard
TC	≤ 4 (155)	≤ 5 (190)
LDL	≤ 2 (80)	≤ 3 (115)

LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TG: Triglyceride, TC: Total cholesterol

true prevalence of statin intolerance in the HIV-infected population. For example, in one study rhabdomyolysis was diagnosed in patients with non-cardiac CK elevation ≥1000 IU/L[55], whereas in another study rhabdomyolysis diagnoses required a CK level of 500 U/L or greater[36]. As a result, Silverberg et al. determined that three out of 829 HIV-infected patients suffered from rhabdomyolysis, while none of the patients had myalgia, myositis, or myopathy[36]. In the retrospective cohort study of Singh et al., an elevation in CPK level was the most common potentially serious toxicity (15 patients, 2.2% of all study participants): five patients had CPK-level elevations between 1000 and 10,000 U/L and one patient had an elevation > 10,000 U/L[56]. No reports of rhabdomyolysis or other symptomatic side effects were found in a randomized trial of Aberg et al.[57].

Adherence

When it comes to understanding adherence, it is not relevant to distinguish between proven and perceived statin intolerance since adherence is likely to be driven by what patients believe - regardless of whether this is "true" or "false"[44]. Different studies have investigated reasons for being non-adherent to statins by examining patient's specific barriers to appropriate use in the general population. The most common patient-reported reasons in the general population for discontinuing statins were adverse effects (20-42.2%), worries about developing adverse effects (12.7-35%), and doubting the necessity of or lacking knowledge about the efficacy of statins (40-70%)[43,44]. Concerns about medication interaction were also reported[44]. Furthermore, wider prescription of statins in primary prevention where the benefits may be less obvious to patients, especially in the short-term, may also contribute to greater non-adherence and discontinuation[47].

So how does this relate to HIV-positive patients? Concerning adherence, considerably less is known in the HIV-infected population. Based on current evidence, patients discontinue statins either due to adverse events or due to unknown reasons[56]. In the retrospective cohort study of Singh et al., discontinuation of statin therapy due to adverse events was rare with similar rates across the three commonly used statins (7.3% for atorvastatin, 6.1% for atorvastatin, and 5.3% for rosuvastatin) and 7.2% discontinued statins for unknown reasons[56]. While no reports of rhabdomyolysis or other symptomatic side effects were found a randomized trial of Aberg et al., four patients discontinued therapy. Strikingly, three out of these four patients were receiving fenofibrate instead of statin therapy. One other study showed that HIV-infected patients were less likely to become non-adherent to lipid-lowering therapy than patients without HIV-infection (22.0% vs. 27.3%) despite higher rates of adverse events[36].

The findings above underscore that it is important to recognize and classify side effects correctly because in most instances side effects are not necessarily causally related to statin therapy. Furthermore, some patients discontinue statin therapy without any symptoms or laboratory abnormalities at all.

The study of Ou et al. stratified HIV-infected patients by medication adherence in statin therapy. Although they did not examine reasons for being (non-)adherent, they showed that HIV-infected patients who had adhered to statin therapy had a lower CVD risk compared to non-adherent patients[32]. It is important to distinguish between both proven and perceived statin intolerance; on the one hand, serious adverse effects, such as rhabdomyolysis, could lead to death[58], whereas on the other hand, the benefits of proven cardiovascular risk reduction with statins outweighs mild-to-moderate and/or perceived adverse effects.

Interaction

A possible explanation for real side effects lies in drug-drug interactions between statins and cART leading to higher plasma statin levels than expected[59]. Of particular importance is the interaction between drugs that inhibit the CYP3A4 metabolic pathway. The CYP3A4 isoenzyme is the most prevalent isoenzyme in the cytochrome P450 enzyme system, and statins that are metabolized through cytochrome P450 3A4 include atorvastatin, simvastatin, and lovastatin. Rosu-

vastatin and the less efficacious statins fluvastatin and pravastatin have less potential for interaction and the associated changes in plasma concentration since these drugs are metabolized by CYP2C9 (rosuvastatin and fluvastatin) or have non-CYP metabolization (pravastatin)[40].

Since drug-drug interactions between statins and cART may lead to higher plasma concentrations, HIV-infected patients are thought to be more prone to develop side effects. Several studies suggest a dose-dependent association between statins and SAMS[60,61]. In the HIV-infected population, it is, therefore, often recommended to start with the lowest possible statin dose and to monitor closely for adverse effects[62,63], but there is no evidence to support the assumption that the risk of muscle symptoms differs significantly according to statin intensity. Indeed, a meta-analysis did not find a significant dose-dependent association between statins and the risk of musculoskeletal complaints[64].

In discussion with patients who believe they are having side effects, it is important to evaluate the likelihood that the symptoms are causally related to statin therapy or some other cause. In the study of Silverberg et al., HIV-infected patients were not prescribed the same statin intensity or regime as patients without HIV-infected to avoid potential drug-drug interaction. Still, a discontinuation rate of 22% was observed within 12 months[36]. This fits with perceived statin intolerance rather than proven statin intolerance. Looking at different clinical trials and observational studies in the general population, the difference between proven and perceived statin intolerance becomes even clearer: a high rate of muscle and other symptoms attributed to statins are reported in both observational studies and clinical practice. In sharp contrast; however, randomized controlled trials have shown similar muscle symptoms in the statin and placebo groups[65]. For example, Gupta et al. described that the rate of muscle-related side effects increases when patients and their doctors are aware that statin therapy is being used while no increase in side effects was seen during the double-blind phase of the study[65]. This apparent discrepancy is to a large degree explained by the nocebo effect, which is the inverse of the placebo effect. The nocebo effect is defined as "adverse events, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention, or a nonmedical situation"[66]. In this manner, a harmless drug can be injurious.

Suggested solutions for narrowing the statin treatment gap

Addressing the nocebo effect

The expectations of harm from a drug can be powered by many factors, such as increased media coverage of drugs and their perceived side effects[47]. In the current age of internet and social media with its global reach and quick dissemination, the risk of nocebo has increased[67]. More importantly, the principle of informed consent may reinforce the nocebo effect since it obligates clinicians to explain possible side effects when prescribing a drug[68].

Clinical management of the nocebo effect, first of all, includes awareness and recognition by clinicians. Recognition of the nocebo effect is challenging though due to their often-close links to known side effects. Therefore, it is rarely possible to evaluate the precise contribution of the nocebo effect. Shaping patients' expectations of the potential side effects of statins and discussing media coverage may reduce the appearance of the nocebo effect. A randomized controlled study, which aimed to investigate whether nocebo effects can be reduced, has shown that nocebo effects can be minimized and even reversed by conditioning with verbal suggestion[69]. Negative expectations formed from exposure to media warnings about health risks can be reversed or diluted as well by accessing positively framed health information[67].

It is expected that minimizing the nocebo effect may decrease the occurrence of perceived side effects in the HIV-population as well. In addition, the development and successful introduction of novel classes of antiretroviral drugs have led to alternatives with less drug-drug interactions, which may increase statin prescription and adherence among HIV-infected patients. Is this the future way to go?

Changes in antiretroviral therapy

A general strategy considered in patients with significant cART-induced dyslipidemia is switching cART away from those that may affect the dyslipidemia[26]. Many of the "older" antiretroviral drugs have dyslipidemic properties[26], which tends to be most marked with HIV PI's ritonavir and ritonavir-boosted lopinavir[70]. Although NNRTI's induce less dyslipidemia than PI's, both efavirenz and most NRTI's have dyslipidemia effects[70]. New antiretroviral classes have significantly changed the HIV treatment armamentarium thereby

greatly facilitating the process of managing cART-induced dyslipidemia.

The introduction of integrase strand transfer inhibitors (INSTI's), quickly shifted treatment paradigms due to its superior efficacy in combination with an excellent safety profile[71,72]. Rockstroh et al. compared 3 years of antiretroviral therapy with different treatment strategies and showed that raltegravir was associated with fewer drug-related clinical adverse events and significantly smaller elevations in LDL-C levels compared to efavirenz[73]. Newer additions, dolutegravir and elvitegravir have a similar favorable safety and tolerability profile and also have little effect on lipid profile[74,75]. This applies to the most recent addition bictegravir as well[76]. Due to its efficacy, its safety and its "lipid-friendly" characteristics, INSTI's are currently preferred first-line antiretroviral therapy in HIV-infected patients[77].

In addition, INSTI's solve the problem of CYP-induced interactions between statins and antiretroviral therapy as both raltegravir and dolutegravir are not eliminated by a substrate of cytochrome P450 enzymes, but mainly through hepatic glucuronidation[78,79]. Due to this, the clinical need for statins with low drug interaction potential has become less urgent. Although a potential drug-drug interaction with through the glucuronidation metabolic pathway was suspected, a healthy volunteers study showed no significant interaction between pravastatin and raltegravir[80]. Up to the present, no data have been published about the concomitant use of dolutegravir and statins.

Bictegravir, which is currently only licensed in the US, is a substrate of CYP3A4 and glucuronidation (UGT1A1). However, it has low potential to induce drug-drug interactions in healthy volunteers; bictegravir is not an inhibitor or inducer of CYP3A4 or UGT1A1[81]. Since elvitegravir is coformulated with the booster cobicistat, there is inhibition of CYP3A proteins, which may result in increased plasma concentrations of especially simvastatin and lovastatin and in theory more side effects[82,83]. Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of fluvastatin, which is a CYP2C9 substrate[82].

Other new classes of antiretrovirals such as the entry inhibitors maraviroc (a C-C chemokine receptor type 5 inhibitor) and enfuvirtide (a cell fusion inhibitor), although not very often used in clinical practice, both have little effect on plasma lipid levels[84,85]. In addition, neither are inhibitors nor inducers of any of the major CYP450 enzymes[86-88]. Figure 2 provides an overview of the current practical recommendations with regard to concomitant use of statins and antiretroviral therapy.

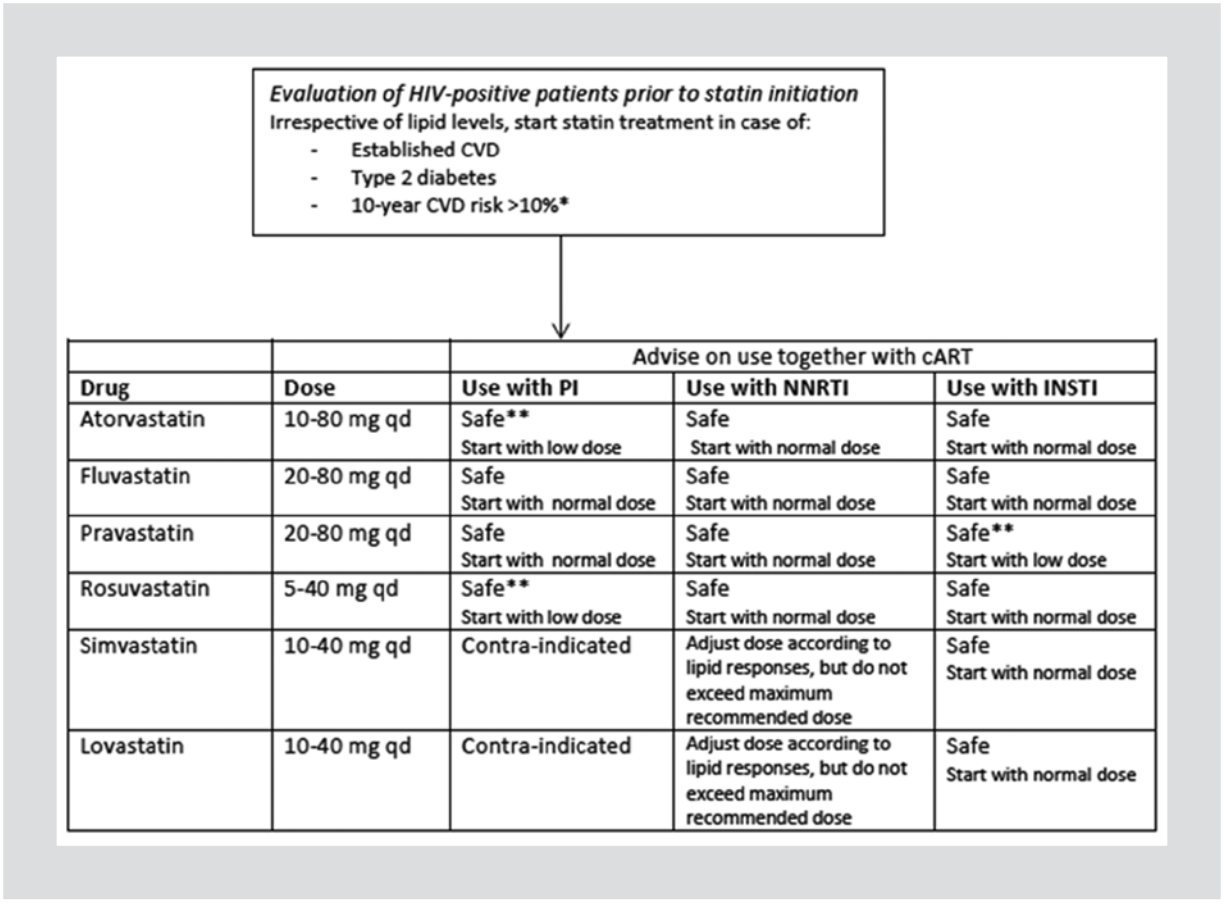
Although the use of newer antiretroviral medication allows physicians to safely treat HIV-infected patients with statins, it is not the only way to circumvent potential drug-drug interactions. If there are still patients who cannot tolerate statins due to perceived/objected side effects, it is also possible to change the lipid-lowering part of the equation.

Changes in Lipid-lowering therapy

Most patients who experience side effects might be able to tolerate a lower dose than the dose that leads to side effects, longer dose intervals, or an alternative statin. In experienced hands, > 90% of patients with statin-associated symptoms can keep on taking statins over the long term and gain the full clinical benefit of statin treatment after a readjustment of statin therapy[47]. In addition, besides statins, there are also other lipid-lowering options. In patients with HIV, there is extensive clinical trial experience with lipid-lowering therapies other than statins, such as fibrates[57] and ezetimibe[89], showing that these therapies are well tolerated and effective. Moreover, research has shown that coadministration of ezetimibe and statins in the general population reduced LDL-C levels 25.8% more than with statin only therapy[90]. The addition of ezetimibe to statin therapy is also efficacious in the HIV-population[89]. It is expected that the availability of the generic form of ezetimibe will have an impact on prescribing patterns, which will shrink the patient pool of statin-intolerant patients.

Over the past years, monoclonal antibodies that inhibit PCSK9 have emerged as a promising new class of drugs that very effectively lower LDL-C levels[91,92]. PCSK9 inhibitors produce a 40-72% reduction in the LDL-C level when combined with a statin or when administered to patients not taking other LDL-C-lowering drugs[93]. Blocking the activity of PCSK9 reduces the degradation of LDL receptors and increases the clearance of LDL cholesterol[94]. Recent data have shown that PCSK9 inhibitors are safe and associated with a reduction in cardiovascular events in the HIV-uninfected population[91].

Since evolocumab and alirocumab are very costly[95], the addition of a PCSK9 inhibitor to standard background therapy often exceeds accepted cost-effectiveness thresholds[96]. PCSK9 inhibitors are currently recommended for people at highest risk of CVD who cannot reduce their LDL cholesterol levels sufficiently on standard lipid-lowering therapy or with proven statin intolerance.



		Advise on use together with cART		
Drug	**Dose**	**Use with PI**	**Use with NNRTI**	**Use with INSTI**
Atorvastatin	10-80 mg qd	Safe** Start with low dose	Safe Start with normal dose	Safe Start with normal dose
Fluvastatin	20-80 mg qd	Safe Start with normal dose	Safe Start with normal dose	Safe Start with normal dose
Pravastatin	20-80 mg qd	Safe Start with normal dose	Safe Start with normal dose	Safe** Start with low dose
Rosuvastatin	5-40 mg qd	Safe** Start with low dose	Safe Start with normal dose	Safe Start with normal dose
Simvastatin	10-40 mg qd	Contra-indicated	Adjust dose according to lipid responses, but do not exceed maximum recommended dose	Safe Start with normal dose
Lovastatin	10-40 mg qd	Contra-indicated	Adjust dose according to lipid responses, but do not exceed maximum recommended dose	Safe Start with normal dose

Figure 2. *Practical recommendations regarding to statin use. *Use DAD, ASCVD, or SCORE-NL models. **Statin and antiretroviral drug share metabolization pathway.*

Practical recommendations regarding to statin use, which are based on what is discussed in this article together with information from the current EACS guideline, are given in figure 2. However, statin intolerance is not discussed in the current EACS guideline and clear guidance on how to assess or approach a patient who is statin intolerant, whether it is perceived or proven, is lacking. We, therefore, propose a therapeutic flowchart for the management of statin intolerance, in which a clear distinction is made between perceived and proven statin intolerance and in which the possible lipid-lowering therapy options are shown in figure 3.

Conclusion

The population of HIV-positive patients has developed into a high-risk population for CVD which necessitates stringent cardiovascular risk management. Despite the availability of efficacious treatment strategies, implementation of guideline supported lipid-lowering therapy with a statin is hampered by perceived, expected, and real side effects and expected interactions with cART. During the past few years, research has shown that side effects often are not attributable to the pharmacological action of a statin. Instead, the nocebo effect is responsible for the majority of the patient reported side effects. Better education of both physicians and patients and using a proper strategy of communication might be beneficial in reducing the nocebo effect, which will subsequently lead to successful initiation and maintaining the patient on a statin. For those patients with real side effects on statin therapy despite changes in the choice of statin, dosage interval and precise dosage or addition, new options in lipid-lowering therapy are available including maximally tolerated dose statin in combination with ezetimibe, as shown in figure 3, or in selected cases, anti-PCSK9 therapy. Finally, newer antiretrovirals do not influence the lipid profile and have a more favorable drug interac-

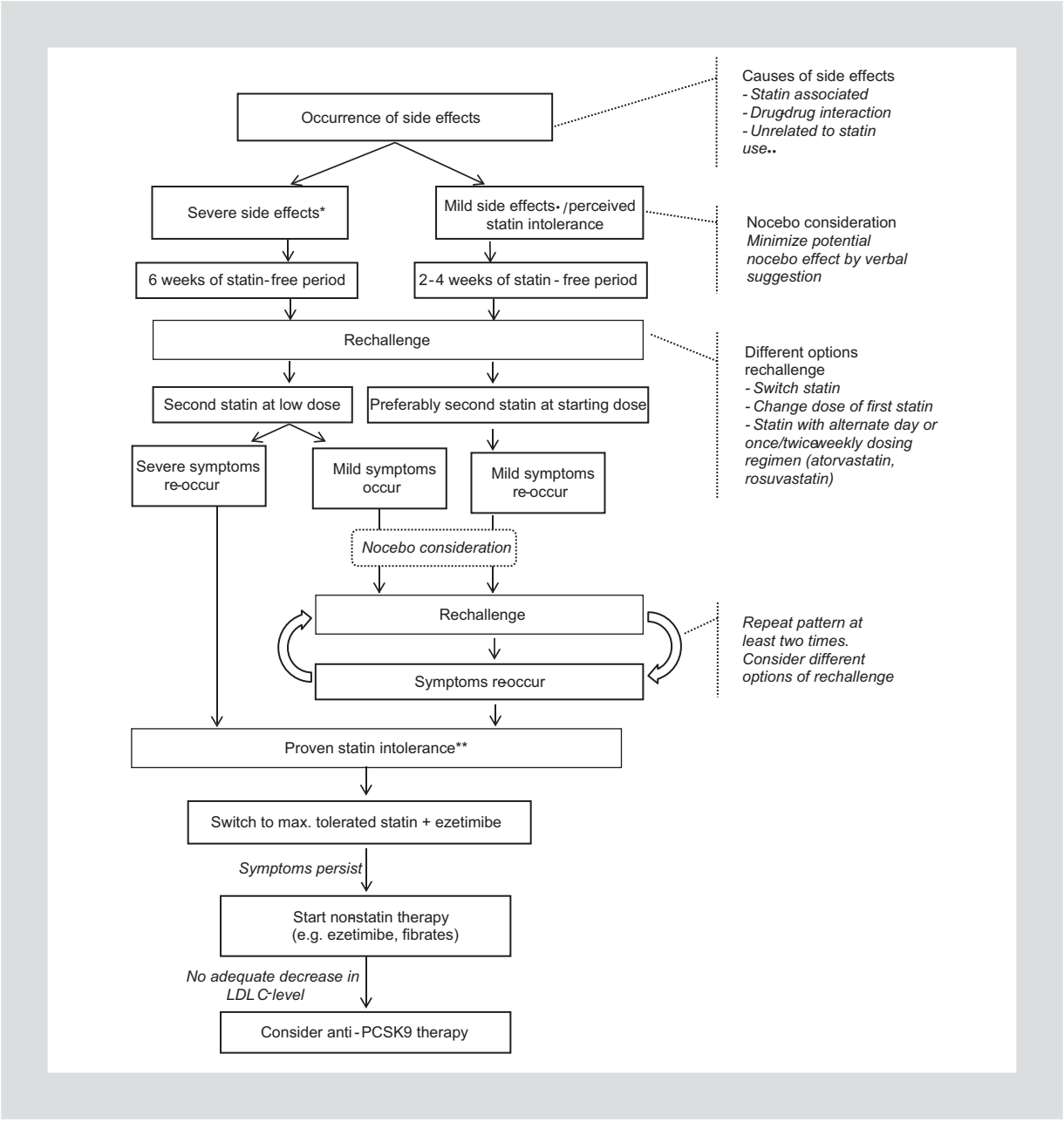


Figure 3. *Therapeutic flowchart. *For example, Rhabdomyolysis, toxic hepatitis. •For example, SAMS, nausea, laboratory abnormalities. ••For example, hypothyroidism, hypovitaminosis D, alcoholism, or excessive physical activity. **Definition can be read 4 pages above in the section Side effects.*

tion profile making concerns about the concomitant use of statins and antiretrovirals unnecessary.

Conflicts of interest

The authors have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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