European AIDS Clinical Society (EACS) Interim Guidance on the Use of Statin Therapy for the Primary Prevention of Cardiovascular Disease in People with HIV

These recommendations have been developed by representatives from the Comorbidities panel of the EACS Guidelines to inform the use of statin therapy for the primary prevention of cardiovascular disease in people with HIV in Europe. The guidance presented here are the best assessment of the evidence at the time of writing, and the key recommendations were formed on this basis. As new evidence emerges, the guidance will be updated accordingly.

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Key Recommendations:

The recommendations below should be combined with discussions on healthy lifestyle measures such as smoking cessation, nutrition, physical activity, weight management and alcohol intake for the prevention of cardiovascular disease (CVD) and other comorbidities [1,2].

We recommend that 10-year CVD risk is estimated annually in people with HIV aged ≥40 years, using the SCORE2 (for people aged 40 – 69 years) or SCORE2-OP (for people aged ≥70 years) tools [2–4].

- When CVD risk estimate is ≥10%:
  - **Statin therapy is indicated** as per the current EACS guidelines [2].
  - Treatment goals for LDL-cholesterol (LDL-c) to reduce CVD risk depend on CVD risk estimation (see page 77, https://www.eacsociety.org/media/guidelines-12.0.pdf) [1,2].
- When CVD risk estimate is 5 to <10%:
  - **We recommend moderate-intensity statin therapy**, options include:
    - Pitavastatin 4mg once daily, where available
    - Atorvastatin 20mg once daily
    - Rosuvastatin 10mg once daily
- When CVD risk estimate is <5%:
  - **Consider moderate-intensity statin therapy** (see options above) if following an evaluation of the risks and benefits, the individual makes an informed decision to proceed.

Background:

Compared to people without HIV, people with HIV have a two-fold higher risk of developing atherosclerotic cardiovascular disease (ASCVD) [5] and ASCVD remains a major cause of death among people with HIV [6,7]. CVD risk estimate calculators designed for the general population underestimate CVD risk in people with HIV [8,9], with a greater degree of underestimation among women with HIV [10]. Furthermore, evidence suggests that the relative increase in CVD risk is greater among women with HIV than with age-matched men with HIV, when compared with people without HIV [7,11–13].

Factors influencing CVD risk among people with HIV include the traditional cardio-metabolic risk factors such as smoking and recreational drugs use which are more prevalent amongst some populations of people with HIV [14,15], immunodeficiency and immune activation due to HIV [16] and specific effects of certain antiretroviral drugs [17,18]. This culminates in ongoing systemic inflammation, evident even in people who are virologically suppressed on effective antiretroviral therapy (ART) [16]. However, it remains unclear to what extent this increased CVD risk can be directly attributed to HIV infection itself, and how much is the result of other contributing factors. Furthermore, structural barriers and disparities in terms of access to prevention, screening and treatment of CVD risk factors are significant factors in the higher risk of development of CVD amongst people with HIV [19].

Current primary CVD prevention strategies recommend optimising traditional risk factors, with a particular focus on smoking cessation and encouraging physical activity, healthy diet, alcohol intake restriction and maintaining a healthy bodyweight [1,2]. In addition, statins are the cornerstone of pharmacological preventative strategies to reduce CVD risk with well-described reduction in CVD events and positive effects on inflammatory pathways. Statins are cheap, widely available and implementation is well-established in many healthcare settings.

Current EACS guidelines already recommend the initiation of statin treatment for the primary prevention of CVD in adults with HIV with a SCORE2 or SCORE2-OP 10-year CVD risk estimate ≥10% [2]. For people intolerant of statin therapy, please refer to the EACS guidelines for alternative lipid-lowering agents [2].

Summary of the evidence

The updated recommendations above are derived from the findings of Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), a Phase 3 global randomised controlled trial of oral pitavastatin 4mg daily compared to placebo in preventing ASCVD in people with HIV receiving ART aged between 40 to 75 years and at low-to-intermediate risk according to 10-year ASCVD risk estimates using the American Heart Association and American College of Cardiology (AHA/ACC) 2013 Pooled Cohort Equation risk calculator with specific thresholds for LDL-cholesterol[20]. A total of 7,769 participants with median 10-year ASCVD risk of 4.5%, enrolled in the trial which demonstrated that compared to placebo, pitavastatin 4mg daily was associated with a 35% reduction in major adverse cardiovascular events (MACE) over a median follow-up of 5.1 years, an effect that was consistently demonstrated across the major subgroups [20,21]. The composite of primary MACE included cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke, transient ischaemic attack, peripheral arterial ischaemia, revascularisation of a coronary, carotid or peripheral artery or death from an undetermined cause. Of note, the absolute risk reduction was greater for people with 10-year ASCVD risk estimates ≥5% compared to those at lower risk at <5%. The 5-year number needed

to treat to avoid one MACE among those with an AHA/ACC CVD risk score >10%, 5–10%, 2.5–<5% and <2.5% was 35, 53, 149 and 199, respectively[20].

In conclusion, the overall findings from the REPRIEVE trial coupled with the observation that CVD risk calculators designed using data from the general population consistently underestimated CVD risk among people with HIV, informed the EACS panel to recommend that moderate-intensity statin therapy for the primary prevention of CVD should be offered to people with HIV aged ≥40 years, using the CVD risk estimate criteria as described in the Key Recommendations above.

EACS strongly supports:

- Involvement of the person under care in the shared decision-making process, including a risk-benefit assessment when considering options for the prevention of CVD.
- taking an individualised approach by considering the individual's underlying risk factors [2] and patient preferences.
- taking a shared care approach between healthcare professionals for the management of people with HIV to live longer healthier lives, by including HIV clinicians, primary care providers and healthcare providers from other specialities.

Specific considerations

CVD risk category thresholds

CVD risk categorisation in Europe (for example using SCORE2, SCORE2-OP) is different from in the USA (using the ASCVD PCE ACC/AHA risk estimation tool). Establishing comparisons of CVD risk category thresholds between SCORE2/SCORE2-OP and the ASCVD PCE ACC/AHA is difficult but overall, the SCORE2 risk estimation tool generally defines higher risk of CVD events at lower thresholds compared to ASCVD PCE ACC/AHA [22].

Table 1: ACC/AHA and ESC (SCORE2/SCORE2-OP) 10-year ASCVD risk categories

ESC Risk Category	SCORE2/SCORE2-OP	ACC/AHA (PCE)	ACA/AHA Risk Category
Low-moderate	<2.5% (age <50y) <5% (age 50-69y) <7.5% (age ≥70y)	<5% (age 40-75y)	Low
High	2.5-<7.5% (age <50y) 5-<10% (age 50-69y) 7.5%-<15% (age ≥70y)	5%-<7.5% (age 40-75y)	Borderline
Very high	≥7.5% (age <50y) ≥10% (age 50-69y) ≥15% (age ≥70y)	7.5%-<20% (age 40-75y)	Intermediate
		≥20% (age 40–75y)	High

Adapted from Fegers-Wustrow I et al. Comparison of American and European Guidelines for Primary Prevention of Cardiovascular Disease: JACC Guideline Comparison. J. Am. Coll. Cardiol. 2022; 79 [22]
Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; ESC = European Society of Cardiology; PCE = pooled cohort equation; SCORE2 = systemic coronary risk estimation 2; SCORE2-OP = systemic coronary risk estimation 2-older persons; y = years

Rationale for choice and dose of statin therapy recommendations

In the REPRIEVE trial, pitavastatin was selected in part due to the low drug-drug interaction (DDI) potential with commonly used antiretroviral medication [20]. Current evidence supports the treatment effect of moderate-intensity statins for lipid-lowering and on surrogate markers of CVD, and reductions in inflammation and immune activation, including among people with HIV [23–25]. Until more data becomes available, EACS supports the use of at least moderate-intensity statins to include pitavastatin 4mg once daily (where available), and atorvastatin 20mg once daily or rosuvastatin 10mg once daily as alternatives, where pitavastatin is not available.

Prescribing and monitoring

The implementation pathways of statin therapy in people with HIV across Europe is country-dependant. The healthcare professional responsible for initiating and monitoring statin therapy (e.g. primary care provider, HIV clinician or healthcare providers from other specialities) for the primary prevention of CVD should be adequately informed and supported with the implementation of the expanded considerations and recommendations for statin therapy in people with HIV ≥40 years. Statin adherence should be assessed and supported by the healthcare provider prescribing statin therapy. HIV clinicians should also review statin therapy adherence at a minimum on an annual basis when assessing ART adherence.

Public healthcare systems that provide statin therapy for the primary prevention of CVD should consider the enhanced need of people with HIV and facilitate adequate provision of statin therapy in this population.

Treatment goals for pharmacological LDL-cholesterol lowering to reduce CVD risk where 10-year CVD risk estimate is ≥10% depends on the CVD risk estimation strata [1,2].

Drug-drug interactions

The drug-drug interactions (DDIs) between antiretrovirals and statins vary depending on the elimination pathway of statins and the inhibitory/induction potential of antiretrovirals. Among the three recommended moderate-intensity statins, pitavastatin has the lowest potential for DDIs as it undergoes minimal metabolism via the cytochrome P450 (CYP450) enzyme system.

Boosted antiretrovirals increase the exposure of statins to various extent depending on the contribution of CYP3A4 to statin metabolism and depending on their inhibitory effect on the hepatic transporter OATP1B1 (highest inhibition by atazanavir). When possible, atorvastatin should be avoided with boosted atazanavir and should be initiated at the lowest dose with other boosted antiretrovirals. Initiation with the lowest dose of rosuvastatin is also recommended for boosted atazanavir and darunavir.

On the other hand, certain non-nucleoside reverse transcriptase inhibitors (NNRTIs) can decrease the exposure of statins, which may require a dose adjustment of the statin.

Please refer to the EACS guidelines [2] and the University of Liverpool HIV Drug Interactions website (https://www.hiv-druginteractions.org/) for more information about anticipated DDIs between antiretroviral agents and statins.

Adverse effects

Statin therapy is generally well-tolerated and has a favourable safety profile.

However, some statin therapy-related adverse effects have been reported, including:

- **Muscle-related symptoms:** These are the most frequent adverse effects reported with an occurrence rate of 5% - 10% in people taking statin therapy, the majority reporting mild and self-limiting symptoms while severe myopathy and rhabdomyolysis are rare [26].
- **Liver function test abnormalities:** mild elevations in liver enzymes are seen in some individuals taking statin therapy, but these are usually mild, transient and of minimal clinical significance.
- **Incident diabetes:** In a meta-analysis of trials conducted in general population cohorts, the risk of incident diabetes following the initiation of statin therapy is increased in people with [27]:
    - elevated baseline fasting blood glucose level
    - insulin resistance (Homeostatic Model Assessment of insulin resistance (HOMA) >2)
    - increased body mass index (BMI)
    - familial history of diabetes
    - elevated fasting triglycerides
    - prevalent hypertension

  The risks and benefits of initiating statin therapy need to be particularly considered in people with CVD risk <5% but who have these risk factors for the development of diabetes.

Contraindications to statin therapy

Pregnancy and breastfeeding

Statin therapy is not recommended during pregnancy or when breastfeeding due to the potential risk of teratogenicity. Statin therapy should be withheld in women planning to conceive and statin therapy should be discontinued during pregnancy and only restarted once breastfeeding has ceased, if applicable.

Statin therapy should be used with caution in people with:

- a history of liver disease
- excessive alcohol consumption
- moderate or severe renal impairment
- concomitant use of drugs known to be associated with myopathy (e.g. fibrates)

Statin Therapy intensity

Table 2: Spectrum of statin therapy intensity [28]

	Low intensity	Moderate intensity	High intensity
Average LDLc lowering potential	**<30%**	**30 to <50%**	**≥50%**
Pitavastatin	n/a	1-4mg	n/a
Atorvastatin	n/a	10-20mg	40-80mg
Rosuvastatin	n/a	5-10mg	20-40mg
Simvastatin	10mg	20-40mg	n/a
Pravastatin	10-20mg	40-80mg	n/a
Fluvastatin XL	n/a	80mg	n/a
Fluvastatin	20-40mg	40mg twice daily	n/a
Lovastatin	20mg	40-80mg	n/a

All doses are prescribed once daily, except where stated otherwise
Abbreviations: LDLc = low-density lipoprotein cholesterol

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