

BHIVA guidance on the use of statins for primary prevention of cardiovascular disease in people living with HIV v2

22 March 2024

Review date: November 2027

Version control:

- V1 original guidance
- V2 updated in light of comments received via the BHIVA website:
 - Adherence paragraph moved from communication section and combined with paragraph in adherence section.
 - Other changes highlighted.

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Introduction

In cohort studies, compared to the general population or controls without HIV, people living with HIV are at greater risk of atherosclerotic cardiovascular disease (CVD) [1]. There are established national guidelines for the primary prevention of CVD with statins [2]. Because general population CVD risk calculators may underestimate risk in people living with HIV [3], HIV is considered an additional CVD risk factor in the National Institute for Health and Care Excellence (NICE) guidelines [2], but there are no specific recommendations for people living with HIV. REPRIEVE, the largest randomised trial undertaken in people living with HIV, demonstrated a significant reduction in major adverse cardiovascular events (MACE) in participants randomly assigned to pitavastatin 4 mg daily as compared to those receiving placebo [4]. Here we provide rapid guidance on the implications of the REPRIEVE study for clinical practice. Statins are an effective tool to reduce CVD risk but should be considered in the context of holistic lifestyle optimisation with a particular focus on smoking cessation. While current guidelines in primary prevention focus on estimated 10-year CVD risk, the goal of this guidance is to attenuate lifetime not just 10-year risk.

Strategy

The scope, purpose and guideline topics were agreed by the writing group, and the question was defined as 'Is there specific evidence for CVD prevention strategies (e.g. statins) for people living with HIV'. A systematic literature search of Medline, Embase and Cochrane Library databases from January 1995 to August 2023 and conference abstracts from January 2021 to August 2023 was performed. Details of the search question and strategy (including the definitions of populations, interventions, comparisons and outcomes) are available on request. For this rapid guidance, authors included publications of major importance at their discretion.

Using the modified Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system, writing group members assessed and graded the quality of evidence and strength of recommendations included in this rapid guidance.

Recommendations

- We suggest that CVD risk assessment and discussion about pharmacological primary prevention is combined with a holistic approach to lifestyle modifications including smoking cessation and dietary advice, and people requiring further support should be signposted to or referred for appropriate multidisciplinary support (GPP).
- We recommend that CVD risk is assessed using tools recommended by BHIVA monitoring and national guidelines (GPP).
- **We do not recommend imaging as part of CVD risk assessment for primary prevention (GPP).**
- We advise baseline lipid assessment for all people living with HIV (GPP).
- We recommend excluding familial hypercholesterolaemia in all people with total cholesterol greater than 7.5 mmol/L without clear cause or a personal/immediate family history of coronary artery disease below the age of 60 years (Grade 1C).
- We recommend optimising antiretroviral therapy in people at high risk of CVD in line with BHIVA treatment guidelines (Grade 1C).
- We recommend that all people living with HIV aged 40 years or older should be offered a statin for primary prevention of CVD irrespective of lipid profile or estimated CVD risk (Grade 1B).
- We suggest that people living with HIV aged 40 years or older with an estimated 10-year CVD risk of 5% or greater are prioritised for primary prevention with a statin (GPP).
- We recommend pitavastatin 4 mg daily as the first-line choice for primary prevention when it becomes available in the UK (Grade 2A).
- We suggest that atorvastatin 20 mg daily can be used as an alternative statin (Grade 2B).
- We suggest that people on a low-intensity statin should switch to one of moderate intensity if clinically appropriate and tolerated (GPP).
- For people unable to tolerate a statin, we advise offering an alternative lipid-lowering agent in line with national guidelines (GPP).
- It is best practice for statins for primary prevention to be prescribed and monitored in primary care (GPP).

CVD risk assessment in people living with HIV

As mentioned above, CVD risk calculators may underestimate risk in people living with HIV [3]. CVD risk estimation should be based on the latest BHIVA and relevant national guidelines (e.g. NICE [2] and Scottish Intercollegiate Guidelines Network [SIGN] [5]) so further detail is not provided here.

Although the recommendation for offering statins for primary prevention of CVD is independent of estimated CVD risk, discussing estimated risk with people living with HIV is an important part of shared decision-making with regards to motivation for modification of other risk factors. It may also be helpful to discuss number needed to treat at different CVD risk thresholds (see below).

Although we do not recommend routine imaging, where an individual has a normal computerised tomography coronary angiography (CTCA) and/or coronary artery calcium score (CACs), this can be considered when discussing the relative benefit of starting a statin.

It is reasonable to defer statin initiation with a suggested interval for repeat CTCA/CACS of 5 years.

In addition, although the recommendation to offer a statin is irrespective of lipid levels, excluding familial hypercholesterolaemia requires baseline lipid assessment in all people living with HIV. If this is not available, lipids should be measured prior to statin initiation. Familial hypercholesterolaemia should be considered in all people with total cholesterol greater than 7.5 mmol/L without clear cause or a personal/immediate family history of coronary artery disease below the age of 60 years. Of note treatment of, and low-density lipoprotein (LDL)-cholesterol targets for, familial hypercholesterolaemia differ from recommendations for primary prevention [6].

Summary of evidence

The benefits of statins for primary prevention of CVD are well established and form the basis for existing guidelines [2,5]. Specific evidence for people living with HIV was lacking; REPRIEVE sought to address this. In REPRIEVE, 7769 participants living with HIV at low–moderate CVD risk (median 10-year risk of 4.5% based on the American Heart Association and American College of Cardiology (AHA/ACC) 2013 Pooled Cohort Equation risk calculator with specific thresholds for LDL-cholesterol) and median baseline LDL-cholesterol of 2.8 mmol/L were randomly assigned to pitavastatin 4 mg daily or placebo [4].

The study was terminated early by the Data Safety and Monitoring Board (DSMB) due to a 35% reduction in MACE after a median of 5.1 years follow-up, an effect that was consistent across major subgroups. Notably, the relative reduction in MACE was greater than the 17% decline predicted by the degree of LDL-cholesterol reduction achieved. Although the authors hypothesise that this may be secondary to the pleiotropic effects of statins (such as their anti-inflammatory and immunomodulatory effects) playing a particularly important role for people living with HIV, it is also possible that this observation reflects intervention earlier in the atherosclerotic process [7]. If statins do indeed have important anti-inflammatory effects in people living with HIV, this may have a positive impact on the risk or progression of other age-related comorbidities.

No unanticipated safety concerns were noted at DSMB review with similar adverse events in each arm. Muscle-related symptoms were more common on pitavastatin (although common in both arms) but were mainly mild and led to withdrawal in only 1% of participants, with no difference in grade 3 transaminitis or rhabdomyolysis. Incident diabetes was more common in the statin arm, but rates were no higher than for the general population and the MACE benefits remained for those with diabetes [4].

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 [4].

People for whom a statin is recommended who are already on a moderate-intensity statin can be reassured but those on a low-intensity statin should be advised to switch to one of moderate intensity if clinically appropriate and tolerated. The recommendation to offer a statin to all people living with HIV, including those with an estimated 10-year risk less than 10% is consistent with NICE guidelines [2]: ‘do not rule out lipid modification therapy...

because the person's 10-year QRISK3 score is less than 10% if they have an informed preference for taking a statin or... risk may be underestimated'.

NHS England has produced a flowchart for lipid management for primary prevention of CVD [8] and recommends checking non-fasted lipids 3 months after statin initiation.

The Joint British Societies' (JBS3) consensus recommendations for the prevention of cardiovascular disease outline lipid targets (at the time of writing the recommended target LDL-cholesterol is less than 1.8 mmol/L) [9].

Considerations for implementation and shared decision-making

Shared decision-making and decision tools

- **NICE tool [10]**
- **NHS Scotland tool [11].**

Communication and prescribing

As these recommendations are consistent with existing national guidelines on the use of statins for primary prevention, prescribing should be undertaken in primary care. Clear GP communication, outlining the rationale, recommended dose (considering any drug–drug interactions) and request to check that lipids 3-months post-initiation meet JBS3 targets (LDL-cholesterol <1.8 mmol/L at the time of writing), is crucial.

We suggest considering including the following information when requesting initiation of a statin in primary care: “The recommendation to offer a statin to all people living with HIV, including those with an estimated 10-year risk of less than 10% is consistent with NICE guidelines; NICE advises to not rule out lipid modification therapy if a person's 10-year QRISK3 score is less than 10% if risk may be underestimated, as is the case for people living with HIV”.

If routine monitoring in HIV services reveals suboptimal LDL-cholesterol lowering, this should be communicated to the GP with a suggestion to intensify treatment in line with their usual practice, drug–drug interactions permitting.

People who have not shared their HIV status with their GP, or who are not registered with a GP, should be encouraged to do so. HIV clinics may elect to initiate and/or continue statins where absolutely necessary, depending on local practice and resources.

Adverse events

It is important to note that statins are not recommended in pregnancy or during breastfeeding. Women who are planning to conceive should not be initiated on a statin and statins should be stopped immediately during pregnancy and not restarted until the cessation of breastfeeding, if applicable.

As a class, the most common adverse events associated with statins include myopathy, rhabdomyolysis (both rare with estimated incidences of 5 and 1.6 cases per 100,000 person years, respectively [2]) and liver function test abnormalities. Pitavastatin has been associated with similar safety profiles to comparable doses of atorvastatin, simvastatin and low-dose pravastatin. In the REPRIEVE study the incidence of adverse events was similar in

the pitavastatin and placebo arms [4]. Even when given in higher doses during prolonged treatment, overall rates of adverse events were low [12]. In the REPRIEVE study, the rate of muscle-related symptoms was generally low: 2.3% on pitavastatin versus 1.4% on placebo, with discontinuation in only 1.1% of participants.

There has also been a reported association between new-onset diabetes and statin use; in a meta-analysis of 13 statin trials, treatment with statins was associated with a 9% increased relative risk of incident diabetes with older age identified as a risk factor [13] but absolute risk was low (1–1.2%). Overall, treating 255 people (95% confidence interval 150–852) for 4 years resulted in one extra case of diabetes. Across three large randomised clinical trials, baseline fasting glucose level, body mass index, hypertension and fasting triglycerides independently predicted the development of new-onset type 2 diabetes mellitus [14]. In JUPITER, there was no incident diabetes in individuals randomly assigned to a statin who had no major diabetes risk factors and, by comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5.4 weeks (84.3 vs 89.7 weeks on placebo) [15].

In previous studies, pitavastatin was shown to have a neutral or positive effect on glucose metabolism [16]. In the REPRIEVE study [4], higher incidence of diabetes mellitus was observed in people taking pitavastatin compared to placebo (5.3% and 4.0% of participants, respectively). Notably in other statin trials the MACE benefits of statins were still significant in participants who developed glucose elevations sufficient to reclassify them as having diabetes. There was no apparent treatment effect on glucose levels, and overall the frequencies of incident diabetes mellitus in both arms of the REPRIEVE study were comparable to incidence in the general US population. As excess weight is an important driver of insulin resistance, advice related to ideal weight and appropriate lifestyle modification is critical.

Pitavastatin should be used with caution in people with a history of liver disease, excessive alcohol consumption or moderate or severe renal impairment, or with concomitant use of drugs known to cause myopathy (e.g. fibrates or niacin) [17].

For people unable to take or tolerate a statin, relevant national guidance should be followed. NICE recommends considering ezetimibe [4] and/or bempedoic acid if ezetimibe yields inadequate LDL-cholesterol reduction [18]. NHS England advises following the Accelerated Access Collaborative statin intolerance algorithm [19] and using ezetimibe as an alternative with bempedoic acid added if there is an inadequate reduction in LDL-cholesterol or non-HDL-cholesterol.

Drug–drug interactions

While most statins are metabolised via the cytochrome P450 (CYP450) system and so are at risk of drug–drug interactions with potent inhibitors or inducers, the metabolism of pitavastatin via CYP450 is minimal.

Pitavastatin

- Co-administration of lopinavir/ritonavir, darunavir/ritonavir, efavirenz or cobicistat with pitavastatin may result in minor changes in pitavastatin exposure which are not considered clinically relevant. Co-administration with atazanavir alone has been

observed to increase pitavastatin exposure therefore pitavastatin with boosted or unboosted atazanavir should be started at the lowest possible dose and titrated according to clinical response. Additionally, inhibition of drug transporters by protease inhibitors and cobicistat may inhibit hepatocellular uptake of pitavastatin, leading to decreased efficacy despite increases in exposure. In such cases, optimisation of antiretroviral therapy and removal of protease inhibitors or the pharmacokinetic booster should be considered where possible.

Atorvastatin

- Co-administration of ritonavir- or cobicistat-boosted darunavir or elvitegravir results in increased concentrations of atorvastatin; we advise starting at the lowest possible dose of atorvastatin, not exceeding 40 mg per day and careful safety monitoring.
- Co-administration of ritonavir- or cobicistat-boosted atazanavir with atorvastatin is predicted or proven, respectively, to yield a significant increase in atorvastatin exposure. Co-administration is not recommended but where unavoidable, we advise starting at the lowest possible dose of atorvastatin and not exceeding 10 mg per day.
- Co-administration of lopinavir/ritonavir yields significantly higher atorvastatin concentrations; we advise using the lowest possible starting dose of atorvastatin, not exceeding 20 mg per day and careful safety monitoring.
- Co-administration of efavirenz with atorvastatin leads to variable reductions in plasma concentration of atorvastatin and an increase in atorvastatin dose may be required. We advise monitoring lipid values and adjusting the dose of atorvastatin based on clinical response.

Ezetimibe

- Ezetimibe is glucuronidated by UDP-glucuronosyltransferases (UGTs) and is a substrate of OATP1B1. Atazanavir/cobicistat and atazanavir/ritonavir could potentially increase ezetimibe levels. We advise starting with the lowest possible dose. Close monitoring is recommended.

Bempedoic acid

- Bempedoic acid is glucuronidated by UGT2B7; ritonavir may therefore reduce bempedoic acid concentrations but the clinical relevance is uncertain as several pathways are involved in bempedoic acid elimination.
- Efavirenz may increase bempedoic acid exposure but based on interaction studies with other UGT inhibitors this is unlikely to be clinically significant.

See the Liverpool University HIV Drug Interactions website for further information about drug–drug interactions (hiv-druginteractions.org).

Prescribing and communication

HIV services should assess CVD risk in line with BHIVA monitoring guidelines. Where a statin is recommended for a person this should be communicated to their GP and, where the person decides to start a statin, prescribed by their GP. Any communication should highlight that because people living with HIV are at higher risk of CVD, a different threshold for primary prevention with a statin is recommended and that this is consistent with NICE and SIGN guidelines.

For people not registered with a GP, or who experience barriers in accessing a statin from their GP, HIV clinics should prescribe and monitor accordingly.

Lifestyle optimisation

All individuals should be provided with advice, and signposting, related to lifestyle optimisation including:

- Smoking cessation: the benefit of statins is attenuated in smokers [4].
- Exercise, diet and weight management.
- Alcohol consumption.

Examples of resources include:

- SIGN [11]: general lifestyle advice.
- HEART UK Healthy Living [20].
- NHS website [21]: general lifestyle advice including advice about salt intake and blood pressure.

Adherence

Adherence to antiretrovirals should be reviewed regularly, in line with existing guidance, and the potential impact of additional pill burden discussed, and reviewed regularly, on a case-by-case basis. Both pitavastatin and atorvastatin are once-daily medications which can be taken at any time of the day with or without food. For persons on once-daily antiretroviral therapy, we suggest taking statin medication at the same time as their current antiretroviral therapy.

It is expected that statin adherence assessments should be undertaken by the prescribing service, but we suggest that HIV clinics proactively address adherence on at least an annual basis, ideally when assessing adherence to antiretroviral therapy.

Statin intensity

Based on AHA/ACC classification [22], statins are grouped into low-, moderate- and high-intensity statins (see table).

Statin	Low intensity	Moderate intensity	High intensity
Atorvastatin	n/a	10–20 mg	40–80 mg
Fluvastatin	20–40 mg	80 mg	n/a
Lovastatin	20 mg	40–80 mg	n/a
Pitavastatin	n/a	1–4 mg	n/a
Pravastatin	10–20 mg	40–80 mg	n/a
Rosuvastatin	n/a	5–10 mg	20–40 mg
Simvastatin	10 mg	20–40 mg	n/a

n/a, not applicable.

Other guidelines

Since v1 of this rapid guidance was published, US guidelines now also recommended initiating a statin for primary prevention in adults with HIV over the age of 40 with an

estimated CVD risk of 5% or greater and favour initiating a statin where estimated risk is less than 5% [23].

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