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Evidence-based review of statin use in patients with HIV on antiretroviral therapy

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ABSTRACT

Introduction: As a result of improved safe and effective therapeutic options for human immunodeficiency virus (HIV), life expectancy of those living with HIV is increasing leading to new challenges (e.g., management of chronic diseases). Some chronic diseases (e.g., cardiovascular disease [CVD]), are up to two times more prevalent in patients with HIV. Statins are a mainstay of therapy for prevention of CVD; but, clinicians should be aware that not all statins are appropriate for use in the HIV population, especially those receiving antiretroviral therapy (ART). The purpose of this article is to review the pharmacokinetic and clinical data for statin therapy in HIV-infected patients receiving ART.

Methods: A systematic literature search using PubMed and MEDLINE databases was performed using each statin drug name combined with HIV, pharmacokinetics, AIDS, and/or human immunodeficiency virus. English language trials published from 1946 to November 2016 were considered, and results were limited to clinical efficacy trials.

Results: In general, atorvastatin and pravastatin are safe and effective for patients treated with protease-inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor-based ART. Rosuvastatin is generally considered safe if started at a low dose, but should be avoided if possible in patients receiving PI-based ART. Pitavastatin has limited supporting evidence, but appears safe for use based on its pharmacokinetic properties and low number of drug interactions. Fluvastatin, lovastatin, and simvastatin should be avoided in patients receiving ART due to drug interactions, adverse events, and/or limited clinical data.

Conclusion: Clinicians need to be familiar with the intricacies of statin selection for the prevention of CVD in patients with HIV on ART.

Contents

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Introduction

Epidemiology of human immunodeficiency virus

Globally, 36.9 million persons are living with human immunodeficiency virus (HIV) [1]. Alarmingly, only 53% have been diagnosed, 41% are on antiretroviral therapy (ART), and 32% are virologically suppressed with HIV RNA viral loads <1000 copies/mL. In the United States at the end of 2012, an estimated 1.2 million individuals 13 years of age and older were living with HIV, of which 12.8% were undiagnosed [2]. The rate of virologic suppression in the US is poor at best at 30%, despite advancements in medical treatment [3]. This is comparable to sub-Saharan Africa (32%), but much lower than Switzerland or France (68% and 52%, respectively).

Life expectancy of HIV-infected individuals

The life expectancy of an HIV-infected patient has increased significantly over the past 30 years [4], from less than 40 years in the late 1990's to over 50 years by the end of 2011 [5]. Unfortunately, a 13.8 year gap in life expectancy persists between HIV-positive and HIV-negative people. Lower rates of life expectancies have been observed in blacks, individuals co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), intravenous drug abusers, and smokers. Earlier initiation of ART, particularly in patients with CD4+ T-helper cells $\geq$500 cells/mcL, increases life expectancy. The median age of patients receiving ART is expected to increase from 43.9 years in 2010, to 56.6 years in 2030, according to data from the ATHENA cohort [6]. Furthermore, the percentage of HIV positive patients aged 50, 60, and 70 years and older is expected to increase from 28% to 73%, 8% to 39%, and 8% to 12%, respectively. The cause of death in HIV-infected patients has shifted for those treated with ART, however. While some continue to die of acquired immunodeficiency syndrome (AIDS), an increasing percentage is due to non-AIDS-defining malignancies, cardiovascular, and hepatic diseases [7].

Incidence of cardiovascular disease

As of 2010, 19% of HIV-infected patients in the Netherlands were diagnosed with cardiovascular disease (CVD); this is expected to increase to up to 78% by 2030 [6]. The increasing incidence of CVD is likely the result of higher rates of CVD risk factors, ART-related metabolic complications, and a longer life expectancy.

The prevalence of CVD morbidity and mortality in HIV-infected patients has consistently been observed to be 1.5- to 2-times greater than negative controls, particularly in those greater than 45 years of age [8–11]. Furthermore, infection with HIV is independently associated with an increased risk of CVD due to inflammation, activation and dysfunction of the immune system, and immunosenescence [12,13].

Significance of drug interactions and metabolic consequences of use

Despite virologic suppression, the higher incidence of CVD persists [14], prompting many studies on the association between ART and CVD [11,15,16]. Overall, the extent to which ART contributes to the increased risk of CVD is largely unknown, but likely differs with individual ART drugs. Metabolic changes, including lipodystrophy, insulin resistance, and dyslipidemia, are typically associated with protease inhibitors (PIs), but recent evidence suggests that this may no longer be the case with newer PIs [8]. Neither nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nor integrase strand transfer inhibitors (INSTIs) appear to have an association with deleterious lipid abnormalities or CVD.

Dyslipidemia occurs in up to 80% of HIV-infected patients, and <10% of these patients receive statin therapy [17,18]. One barrier that may explain low rates of statin use is the significance of drug interactions with ART and concomitant statin therapy [19,20]. Most drug interactions with ART occur via the cytochrome P (CYP) 450 system, with PIs inhibiting CYP3A4, while the majority of NNRTIs induce this isoenzyme [21]. Pharmacokinetic properties of statins vary significantly between individual drugs [8,22]. Most statins are primarily metabolized through CYP3A4, with minimal CYP2C9 involvement, to produce pharmacologically active metabolites. The potential for drug interactions exists because many statins are substrates for CYP3A4. Depending on the concomitant medication, serum concentrations of statins may vary, leading to higher rates of adverse events or decreased lipid lowering properties.

Benefits of statin use for CV disease

Statins competitively inhibit hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase impairing cholesterol biosynthesis and decreasing hepatic cholesterol concentrations [14,22]. These actions result in decreased cholesterol in plasma and cell membranes, explaining their widespread use in the primary and secondary prevention of CVD. Statins also have anti-inflammatory effects by decreasing circulating concentrations of pro-inflammatory cytokines, improving endothelial function, and stabilizing coronary plaques [22].

The Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was released by the American College of Cardiology/American Heart Association (ACC/AHA) in November 2013, to replace the outdated Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [23,24]. The new guidelines eliminated LDL-cholesterol (LDL-C) targets, and created 4 groups of patients that could benefit most from statin therapy: patients with atherosclerotic cardiovascular disease (ASCVD), patients with LDL-C $\geq$190 mg/dL, patients age 40–75 years with diabetes mellitus and LDL-C of 70-189 mg/dL without ASCVD, and patients age 40–75 years with LDL-C of 70-189 mg/dL and an estimated 10 year ASCVD risk of $\geq$7.5% without ASCVD or diabetes mellitus. Based on these changes, statin therapy is now recommended for a much larger percentage of the general patient population.