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Pitavastatin as the preferred statin for control of dyslipidemia in patients with HIV infection using antiretrovirals

Pitavastatina como estatina de escolha para o controle da dislipidemia em pacientes infectados pelo HIV em uso de antirretrovirais

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Abstract

Objective: To elucidate the use of pitavastatin as the preferred lipid lowering agent for dyslipidemia and cardiovascular risk in patients with HIV infection. **Methods**: A comprehensive search was conducted on the PubMed and Virtual Health Library (VHL) using the following descriptors in English and Portuguese: “Pitavastatin”, “HIV”, “Statins”, “Infected by HIV”, “Dyslipidemia”, and “Antiretrovirals”. A total of 46 articles were identified, and nine (six from PubMed and three from VHL) were included. **Results**: Antiretroviral therapy significantly changes lipid parameters in patients with HIV infection, justifying its association with statins. However, some antiretrovirals can inhibit the cytochrome P450 3A4 enzyme, which metabolizes most statins. In this context, pitavastatin is preferred since it is mainly metabolized by glucuronidation and is more effective in reducing low-density lipoprotein cholesterol and inflammatory markers than pravastatin, which is also metabolized by glucuronidation. **Conclusion**: Pitavastatin is the preferred lipid lowering agent for dyslipidemia in patients with HIV infection due to its low drug interaction and high efficacy in reducing lipids and inflammatory markers.

Keywords: Antiretrovirals; HIV; Hyperlipidemia; Hypolipidemic; Statins.

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Resumo

Objetivo: Justificar o uso da pitavastatina para o controle lipídico e redução do risco cardiovascular em pacientes infectados pelo HIV. **Métodos**: Foram realizadas buscas na PubMed e na Biblioteca Virtual em Saúde (BVS), com uso dos seguintes descritores, em inglês e português: “Pitavastatina”, “HIV”, “Estatinas”, “Infectados pelo HIV”, “Dislipidemia” e “Antirretrovirais”. Foram encontrados 46 artigos, reduzidos, após o refinamento, a nove (seis da PubMed e três da BVS). **Resultados**: O uso de antirretrovirais (ARV) altera significativamente o perfil lipídicode pacientes infectados pelo HIV, sendo necessária a associação com uma estatina. No entanto, a maioria das estatinas são metabolizadas pelo sistema do citocromo P450 3A4, o qual é inibido por alguns ARV. Nesse contexto, destaca-se a pitavastatina, visto que ela é metabolizada, primariamente, por glucoronidação. Além disso, comprovou-se que esta estatina reduziu mais significativamente os marcadores inflamatórios e os níveis do LDL-c, do que a pravastatina, cuja metabolização é através do mesmo mecanismo. **Conclusão**: A pitavastatina é, preferencialmente, a estatina de escolha para corrigir a dislipidemia em pacientes infectados pelo HIV, devido às suas mínimas interações medicamentosas e maior redução lipídica e dos marcadores inflamatórios.

Palavras-chave: Antirretrovirais; HIV; Hiperlipidemia; Hipolipemiantes; Estatinas.

INTRODUCTION

The human immunodeficiency virus (HIV) infection causes dysfunction of TCD4+ lymphocytes, intense inflammatory and coagulative processes (especially within the vasculature), and increases the immune response (i.e., macrophage recruitment for viral destruction)[1]. Considering the chronic nature of this infection, antiretrovirals (ARV) should be used continuously to delay and alleviate this pathophysiological process[2].

Patients with HIV infection using ARV commonly have an increased risk of developing dyslipidemia and cardiovascular diseases (CVD), which are the main cause of mortality in this population[3]. In this sense, statins are recommended to reduce serum lipid levels and risk of CVD since they are inhibitors of the 3-hidroxi-3-methyl-glutaril-CoA (HMG-CoA) reductase and directly affect cholesterol synthesis[4].

Patients with HIV infection receiving ARV (especially protease inhibitors [PI]) need caution on using statins since most of them interact with PI due to similar metabolism pathways, which may change the glycemic parameter[5]. However, pitavastatin does not interfere with glycemic parameters, interacts less with ARV, and has greater potential to reduce lipid and inflammatory markers than other statins[6].

Considering the relevance of pitavastatin in treating dyslipidemia and reducing CVD in patients with HIV infection using ARV, this study aimed to elucidate its use as a preferred medication in this population.

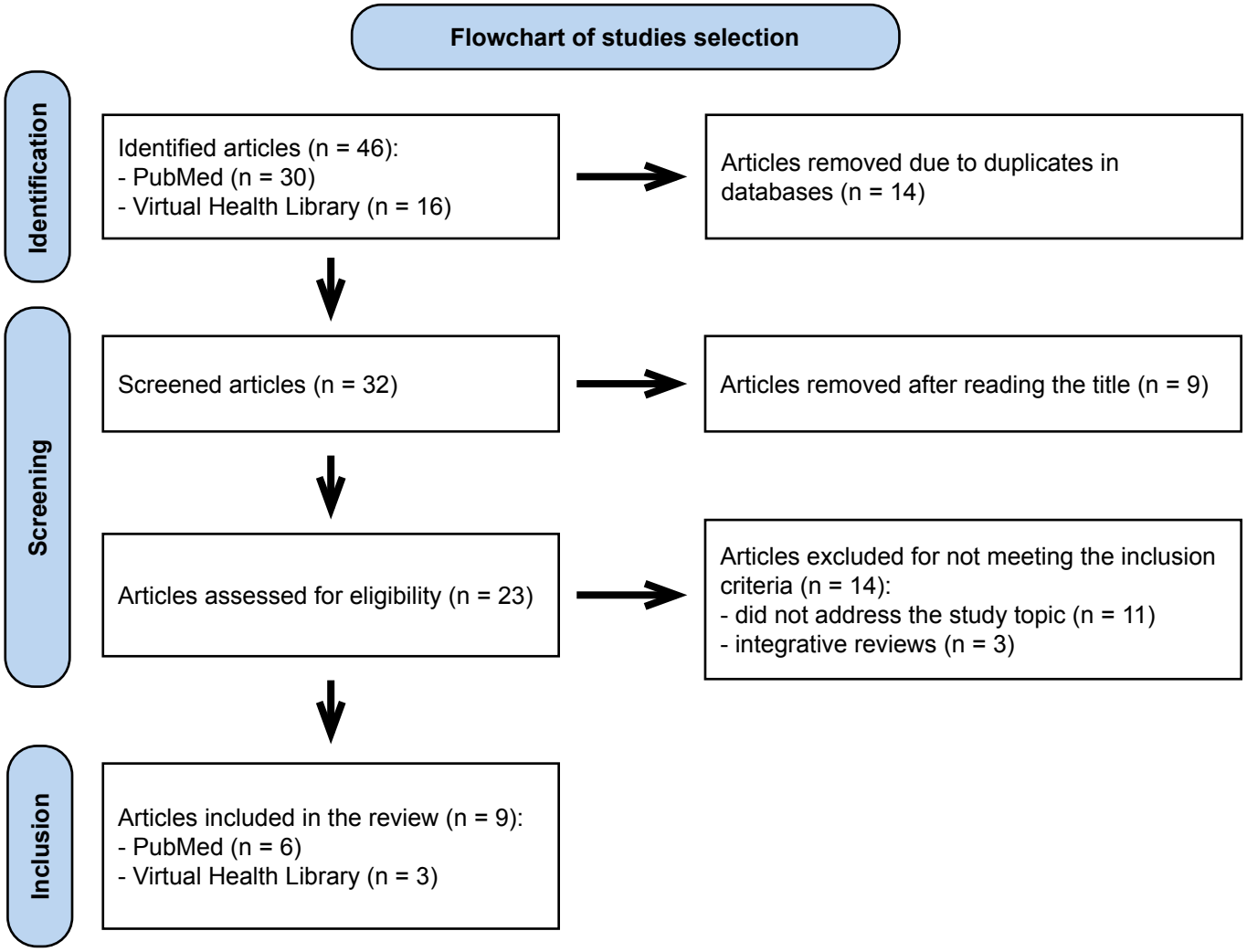
METHODS

This integrative literature review used the PubMed and Virtual Health Library databases.

The following free terms (FT) and Health Sciences Descriptors (DeCS) with Boolean operator (AND) were used as search strategy in Portuguese and English: “pitavastatin” (FT) AND “HIV” (DeCS); “statin” (DeCS) AND “HIV”; “statin” AND “HIV infected” (DeCS); “HIV” AND “dyslipidemia treatment” (FT); “HIV infected” AND “dyslipidemia” (FT); “statin” AND “antiretroviral” (DeCS).

Articles in English or Portuguese addressing the study topic (statins and HIV), studying pitavastatin in patients with HIV infection treated with ARV, dyslipidemia in patients with HIV infection, and interaction between ARV and statins were included. The following articles were excluded: unrelated to the inclusion criteria; not addressing statins or pitavastatin in patients with HIV infection treated with ARV; published more than eight years ago; or integrative reviews. A total of 46 articles were identified, and nine (six from PubMed and three from the Virtual Health Library) were included after screening (Figure 1).

Figure 1. Flowchart of studies selection



Source: The authors

RESULTS

Table 1. Integrative table with the included articles

PITAVASTATIN AS THE PREFERRED STATIN FOR CONTROL OF DYSLIPIDEMIA IN PATIENTS WITH HIV INFECTION USING ANTIRETROVIRALS				
No.	**Title**	**Authors and publication year**	**Study design**	**Objective**
01.	"Effects of Pitavastatin on Lipid Profiles in HIV-Infected Patients with Dyslipidemia and Receiving Atazanavir/ Ritonavir: A Randomized, Double-Bind, Crossover Study"	Wongprikorn A et al., 2016	RCS	To determine the efficacy and safety of pitavastatin in patients with HIV infection and dyslipidemia receiving atazanavir and ritonavir therapy.
02.	"Lipid-lowering therapy in HIV-infected patients: relationship with antiretroviral agents and impact of substance-related disorders"	Bednasz C et al., 2016	Cohort	To examine the relationship of substance-related disorders with ARV therapy and lipid lowering agents in patients with HIV infection.
03.	"Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV"	Toribio M et al., 2017	RCT	To compare the effects of pitavastatin and pravastatin on markers of systemic immune activation and arterial inflammation in patients with HIV infection.
04.	"Pitavastatin versus pravastatin in adults with HIV infection and dyslipidaemia (INTREPID): 12 week and 52-week results of phase 4, multicentre, randomized, double-bind, superiority trial"	Aberg JA et al., 2017	ECIR.	To evaluate the safety and efficacy of pitavastatin compared with pravastatin in adults with HIV infection and dyslipidemia.
05.	"Assessing statin effects on cardiovascular pathways in HIV using a novel proteomics approach: Analysis of data from INTREPID, a randomized controlled trial"	Toribio M et al., 2018	RCT	To analyze the hypothesis that pitavastatin leads to greater changes in the cardiovascular system of patients with HIV infection.
06.	"Rationale and design of the Mechanistic Substudy of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE): Effects of pitavastatin on coronary artery disease and inflammatory biomarkers"	Hoffmann U et al., 2019	RCT	To evaluate the effects of statin on CVD in patients with HIV infection and improve the understanding of results from the REPRIEVE study.

07.	"Cardiovascular risk and response to lipid-lowering therapy in patients with HIV infection according to different recommendations"	Pawlos A et al., 2020	Case-control	To estimate the risk of CVD in patients with HIV infection using the Data Collection on Adverse Effects of Anti-HIV Drugs, Systematic Coronary Risk Evaluation, and Framingham scales. Also, to evaluate the achievement of the therapeutic goal and lipid lowering therapy according to the European AIDS Clinical Society 2019, Polish AIDS Society 2019, and European Society of Cardiology/European Atherosclerosis Society 2019 Dyslipidemia guidelines.
08.	"Real-life management of drug-drug interactions between antiretrovirals and statins"	Courlet P et al., 2020	Cohort	To evaluate the interactions between ARV and statins in patients with HIV infection, considering the serum level of statins, compliance with dosing recommendations, and achievement of lipid targets.
09.	"Effect of Statin Use on Inflammation and Immune Activation Biomarkers in HIV-Infected Persons on Effective Antiretroviral Therapy"	Hussain SK et al., 2020	MCT	To investigate the association of statins and serum levels of immune activation markers in patients with HIV infection receiving ARV therapy.

RCS, randomized control study; ARV, antiretroviral; RCT, randomized clinical trial; CVD, cardiovascular disease; MCT, multicenter clinical trial

Source: The authors

Table 2. Integrative table with results and conclusions of the included articles

PITAVASTATIN AS THE PREFERRED STATIN FOR CONTROL OF DYSLIPIDEMIA IN PATIENTS WITH HIV INFECTION USING ANTIRETROVIRALS			
No.	**Author and year**	**Results**	**Conclusion**
01.	Wongprikorn A et al., 2016	Patients (n = 12) of each group received pitavastatin for 12 weeks. The treatment reduced total cholesterol, LDL, and TG and increased HDL compared with the placebo. Liver enzymes and creatine phosphokinase levels had no significant changes.	Pitavastatin reduced lipid parameters without causing hepatotoxicity or increasing creatine phosphokinase levels compared with placebo.

02.	Bednasz C et al., 2016	Smoking was prevalent in patients with substance-related disorders. Statins were the most used lipid lowering agent (66%), followed by fibrates. The type of ARV might not affect the treatment with lipid lowering agents, and lopinavir was the most prescribed for substance-related disorders.	Statins were the main treatment for dyslipidemia in patients with HIV infection, followed by fibrates. Smokers with substance-related disorders had greater risk of metabolic changes, and lopinavir was the main ARV used. The management of dyslipidemia in this population needs to be optimized due to the low use of lipid lowering agents.
03.	Toribio M et al., 2017	Patients received pitavastatin (n = 126) or pravastatin (n = 126). Before treatment, the mean LDL levels was 153 mg/dL, HIV-1 viral load was 1.1 ± 0.2 copies/mL, and TCD4+ lymphocytes count was 580 cells/μL. After 52 weeks, pitavastatin reduced sCD14, oxidized LDL, and Lp-PLA2 more than pravastatin.	Pitavastatin (4 mg/day) reduced markers of immune activation and arterial inflammation more effectively than pravastatin (40 mg/day) in patients with HIV infection in 52 weeks. However, whether immune modulation by pitavastatin mitigates the risk of CVD in this population needs to be elucidated.
04.	Aberg JA et al., 2017	Pitavastatin (n = 126) significantly reduced LDL levels (31.1%) compared with pravastatin (n = 126; 20.9%). Patients receiving pitavastatin (n = 85) and pravastatin (n = 88) reported adverse effects, and six and five dropped out, respectively. Seven patients receiving pitavastatin had severe effects (e.g., atrial septal defect and heart failure), and three receiving pravastatin had stroke, coronary artery arteriosclerosis, acute myocardial infarction, and muscle hemorrhage.	The INTREPID study supported pitavastatin as the preferred treatment for dyslipidemia in patients with HIV infection.
05.	Toribio M et al., 2018	The mean age of the patients was 49.5 ± 8.0 years old, LDL levels were 155 ± 25 mg/dL, and TCD4+ lymphocyte count was 620 ± 243 cells/mm^3. TFPI, PON3, and LDLR levels reduced, and Gal-4 and IGFBP-2 increased in all patients. TFPI levels related to LDL and Lp-PLA2 differed between pitavastatin and pravastatin groups.	Statins significantly reduced TFPI, PON3, and LDLR and increased Gal-4 and IGFBP-2 levels, which participate in coagulation, redox signaling, oxidative stress, and glucose metabolism. Pitavastatin reduced TFPI more than pravastatin, highlighting the importance of these drugs for patients with HIV infection.
06.	Hoffmann U et al., 2019	The mechanistic substudy had enrolled 805 patients.	This was the first study using coronary computed tomography angiography to evaluate the primary prevention strategy for CVD in patients with HIV infection and elevated risk of coronary artery disease, immune activation, and inflammation. Pitavastatin reduced coronary plaques and interaction with immune activation and inflammation markers, preventing CVD and improving the outcomes.

07.	Pawlos A et al., 2020	Patients with HIV infection (n = 389) had mean total cholesterol of 177.2 ± 36 mg/dL, HDL of 48.9 ± 18 mg/dL, LDL of 103.8 ± 36 mg/dL, TG of 143.3 ± 81 mg/dL, plasma atherogenic index of 0.45 ± 0.3, and non-HDL of 129.2 ± 36 mg/dL. Of these, 360 had an elevated risk for CDV. According to ESC/EAS and PTN AIDS guidelines (respectively), 10.3% and 17.2% of those with very high and 12% and 45.9% of those with high cardiovascular risk achieved therapeutic LDL levels. According to EACS guidelines, they had a 2.5% success rate in secondary and 24.7% in primary prevention. Mean statin doses were 8.75 ± 6 mg for rosuvastatin and 22.35 ± 19 mg for atorvastatin.	Achievement of therapeutic LDL levels according to recommendations was unsatisfactory, especially in patients receiving lipid lowering agents. Treatment of patients with HIV infection was based on low-dose statins.
08.	Courlet P et al., 2020	Patients were treated with rosuvastatin (n = 99), atorvastatin (n = 92), pravastatin (n = 46), and pitavastatin (n = 21). Overdose of the first two led to suboptimal response. High doses of atorvastatin caused insufficient lipid control in patients using protease inhibitors due to low hepatic uptake of statins. Unboosted integrase inhibitors achieved better lipid values. Pitavastatin and pravastatin were also insufficient, regardless of the ARV used and their maximum doses, suggesting lower efficacy than the first two statins.	Suboptimal management of drug interactions and statin overdose was observed in 29% of prescriptions. In patients with refractory dyslipidemia, regimens with integrase inhibitors or treatment with rosuvastatin or atorvastatin were recommended.
09.	Hussain SK et al., 2020	Of 1031 patients with HIV infection, 31.5% were receiving statins and had lower levels of IP-10, IL-10, and IL-12p70 than those not using statins.	Statins reduced the levels of high-sensitivity C-reactive protein, IL-12p70, IL-6, and markers of immune activation and inflammation in patients receiving ARV therapy without aspirin, which may reduce the burden of disease.

LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; LpPLA2, lipoprotein-associated phospholipase A2; TFPI, tissue factor pathway inhibitor; PON3, paraoxonase 3; LDLR, LDL receptor; Gal-4, galectin-4; IGFBP-2, insulin-like growth factor; ARV, antiretroviral. EACS, European AIDS Clinical Society; PTN AIDS, Polish AIDS Society; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society

Source: The authors

DISCUSSION

Patients with HIV infection have a 1.5 to 2-fold higher risk of developing CVD than those not infected, especially non-calcified atherosclerotic plaques and acute myocardial infarction favored by dyslipidemia and increased arterial inflammation[7,8]. In this context, a study with 389 patients with HIV infection showed that 360 had an elevated risk and 14 developed CVD, including ischemic stroke, acute coronary syndrome, and transient ischemic attacks[9].

Dyslipidemia in HIV infection has multifactorial etiology, such as increased proinflammatory and profibrotic cytokines, lipogenesis, and adverse effects of ARV therapy[10]. These factors are triggered by monocytes, macrophages, and TCD8+ lymphocyte activation, resulting in endothelial dysfunction, hypercoagulation, vascular thrombosis, excessive collagen production, fibrotic remodeling of the left ventricle, and hyperlipidemia[11]. Also, TCD4+ lymphocytes are mainly located in the intestinal mucosa, and their destruction increases the permeability to bacteria and lipopolysaccharides, contributing to inflammation.[12] Thus, chronic inflammation in HIV infection and its mechanisms involved in lipogenesis contribute to visceral obesity and lipohypertrophy, increasing the risk of CVD[11]. Despite the increased susceptibility to CVD, many patients are not properly monitored due to the lack of a multidisciplinary approach and stigmas on HIV infection.

ARV is associated with the pathophysiology of HIV infection and significantly increases serum lipid levels, particularly low-density (LDL), intermediate-density (IDL), and very low-density lipoproteins (VLDL); the latter two are triglyceride-dependent, which are also elevated in this context[13]. In addition, ARV has been associated with increased carotid intima-media thickness, carotid or coronary stenosis, and reduced vascular dilation, contributing to atherosclerotic mechanisms and CVD[11]. These changes are common in ARV therapy with non-nucleoside reverse transcriptase (TrR), proteases, and nucleoside TrR inhibitors[4,14]. Therefore, ARV should be prescribed carefully, individualizing their use and monitoring metabolic effects.

In this sense, lipid lowering strategies (e.g., using statins) are essential for patients with HIV infection, especially those receiving ARV therapy, to reduce its adverse effects on the risk of CVD[15]. In these patients, statins reduce LDL, immune activation, oxidative stress, and inflammatory markers (e.g., soluble CD14 [sCD14], lipoprotein-associated phospholipase A2 [LpPLA2], and oxidized LDL [ox-LDL][6,16].

Statins and ARV are mostly metabolized by the cytochrome P450 3A4 (CYP3A4) system, increasing the risk of drug interactions[17]. However, pitavastatin and pravastatin have distinct metabolisms from other statins, being glucuronidated before metabolized via CYP3A4, interacting less with ARV and safer to treat dyslipidemia than other statins[6]. Considering the immunosuppression and high prevalence of comorbidities in patients with HIV infection, potential drug interactions must be considered to avoid systemic effects.

A study with patients with HIV infection (INTREPID) showed that a 52-week treatment with 4 mg/day of pitavastatin was more effective than 40 mg/day of pravastatin in modulating inflammatory markers (e.g., sCD14, LpPLA2, oxLDL, and LDL-c), which are increased in HIV infection and favors the risk for atherosclerosis[18]. Also, pitavastatin and atorvastatin increased the levels of procollagen C-endopeptidase enhancer (PCOLCE) in patients with HIV infection, which is reduced in this population[16,19]. PCOLCE is an enzyme responsible for cleaving type I and III procollagen and activating C-proteinase, predominantly found in the extracellular matrix of blood

vessels and essential in atherosclerotic processes[19]. However, atorvastatin has a high magnitude of drug interactions and should be prescribed with caution, especially when associated with PI therapy[20,21].

Although PI inhibits CYP3A4 and statin transporters, pitavastatin is minimally metabolized by this enzyme and can be safely used with PI[22,23]. In contrast, simvastatin and lovastatin levels increase due to ARV inhibition of the metabolic system, leading to muscle and liver toxicity and resulting in myopathy and rhabdomyolysis[20,24,25]. Supporting its efficacy, a base-case analysis demonstrated that pitavastatin reduced LDL and total cholesterol (19.1%) and increased HDL (8.9%), preventing CVD and reducing morbidity and mortality in patients with HIV infection[26].

CONCLUSION

Results suggested that pitavastatin was the preferred statin to treat dyslipidemia in patients with HIV infection receiving ARV therapy due to its minimal interactions with ARV and efficacy in reducing markers of immune activation, inflammation, and lipid parameters. Also, these markers should be monitored in patients with HIV infection to choose the most suitable lipid lowering agent, especially considering the interactions with ARV.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

TJMBSV: conceptualization, data curation, research, methodology, management, resources, writing of the original draft, and review and editing. **FAP**: draft review and editing. **ADCF**: conceptualization, supervision, and draft review and editing. All authors approved the final version.

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