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Dyslipidemia Management in Patients under Antiretroviral Therapy: Current Status and Possible Treatments

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ABSTRACT

Introduction: Antiretroviral therapy (ART) is a treatment regimen for HIV-positive persons. The major goal of the therapy is to lower an individual's viral load to an undetectable level, rather than to cure the disease. HAART treatment was connected to elevated total cholesterol, LDL cholesterol, and triglycerides. However, the current treatment of dyslipidemia, as well as its cause in HAART patients, is currently unknown. As a basic guideline, prevention should begin with a change in diet and lifestyle, as well as a change in the ART.

Methods: A systematic literature search was conducted utilizing prominent databases and were thoroughly examined in order to offer information in a clear and orderly manner. Articles that are not relevant to the current and potential treatment of dyslipidemia in antiretroviral therapy patients were excluded.

Results: In PLWH, evolocumab has been found to be safe and effective, but more research is needed on the usage of alirocumab with HAART. Hormone replacement treatment (HRT) has also showed potential, particularly in postmenopausal women, although it should be studied in conjunction with HAART. Despite the fact that leptin and growth hormone have yet to receive FDA approval or large-scale research, they show promise as potential therapy options for HIV-related lipid problems. Thiazoldinedione has been touted as a promising treatment for HAART-induced dyslipidemia. However, findings from numerous trials reveal that it is not as effective or useful as currently available medications, ruling it out for usage in HIV patients on antiretroviral therapy. Finally, the good safety, effectiveness, and tolerance of acipimox and tesamorelin supports further research into their usage in HAART-induced dyslipidemia.

Conclusion: The human immunodeficiency virus has become a chronicaly controllable disease, and one of the elements that must be handled in order to maintain quality of life and lifespan is the cardiovascular risks. Alirocumab, evolocumab, hormone replacement therapy, leptin, growth hormone, acipimox, and tesamorelin are the possible drugs that hold potential for managing HIV dyslipidemia. Due to a lack of data, further clinical trials are needed to investigate improved HAART-induced dyslipidemia management options in order to guarantee that patients living with HIV receive the best possible treatment. This study aims to provide a review on the current management and other possible treatments of dyslipidemia in patients under HAART.

Keywords: Dyslipidemia management**,** Antiretroviral Therapy, HAART/ART

Introduction

Antiretroviral therapy (ART) is a regimen to alleviate the condition of people with HIV. It involves the uptake of a combination of HIV medicines regularly with a goal not to cure the disease, but rather to help these individuals to live a longer and healthier life. A viral load test determines the levels of HIV in a human's blood, the main objective of the therapy is to reduce an individual's viral load to an undetectable level. Maintaining an undetectable level of viral load eliminates the potential risk of transmitting HIV to their HIV-negative partners in sexual intercourse [1]. Effective antiretroviral therapy requires persons with HIV to consume three to four regimens which soar high the potential risk of adverse effects and complications. It causes adverse lipid profiles and increased risk for clinical cardiovascular concerns [2]. Apart from the HIV infection linked with an increased risk of left ventricle (LV) dysfunction, congestive heart failure (CHF) and dilated cardiomyopathy, long-term HAART exposure is also associated with increased atherosclerotic risks [3].

This study focuses on one of the major adverse effects associated with HAART which is dyslipidemia. Dyslipidemia is a condition in which lipids such as cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C) are out of balance[4]. One of the characteristic manifestations of dyslipidemia observed in patients under HAART are severe hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and elevation of low-density lipoprotein (LDL) cholesterol. Presence of these clinical manifestations are an indication of

an increased risk of cardiovascular diseases by up to 70% [5]. Studies revealed that HAART has a relative increase of up to 27% of myocardial infarction in 7 years upon exposure [6].

Presently, only a few features the prevalence of dyslipidemia associated-HAART treatment. In a study conducted by Nery et al. in Central Brazil, 66.7% of the one hundred and thirteen patients under HAART therapy involving different regimens such as nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PIs) presented dyslipidemia. Among the studied group, 53.5% relates to Low HDL, and 36.1% links with high triglycerides (TG). More importantly, 95% of the complication corresponds to PI regimen which is 5.2-fold higher risk than the other treatments compared[7].

Current treatments involve PI to bind with LDL receptors-related protein which is responsible for fat storage and lipid release mechanism. Another method, the NRTI utilizes a prodrug to enter the host body and will be activated by the cellular kinase, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) which acts to reduce the overall polymerase activity[8]. Yet even with the current treatment, the pathogenesis of dyslipidemia in patients under HAART is poorly understood at present[9]. This study attends to the current pharmacologic management of dyslipidemia associated-HAART treatment, as well as the first line of therapy involving statin and non-statin lipid lowering agents, alternative therapies and possible treatment.

Methods

A systematic literature search was done using leading databases and articles were subjected to a thorough analysis for a clear and organized presentation. To ensure the review focused on actual observations of the concept of interest, articles that did not relate to the current and possible treatment for dyslipidemia in patients under antiretroviral therapy were excluded. Articles were evaluated for possible inclusion based on their title and abstract, and references within articles of relevance were examined for additional sources.

Antiretroviral Therapy and its Associated Risks

Antiretroviral therapy has significantly improved HIV-infected people's survival rates. Coronary heart disease has become a significant concomitant ailment as the population lives longer. Dyslipidemia in HIV-positive people is a complicated illness caused by a number of variables, including the virus itself, individual genetic features, and antiretroviral therapy-induced metabolic alterations. Effective treatment of dyslipidemia in this group is critical for decreasing cardiovascular risk, however interactions between antiretroviral therapy drugs and lipid-lowering medicines pose a number of problems.

This usage of highly active antiretroviral treatment (HAART) or combination antiretroviral therapy has improved the prognosis of HIV-positive people substantially [10-11]. With increased life expectancy, non-AIDS defining illnesses account for most morbidity and death in this population [10]. According to studies, HIV-positive persons (both males and females) are at a higher risk of developing cardiovascular disease (CVD) [12-14]. CVD risk is increased by traditional CVD risk factors, including the pathogenesis of HIV infection and antiretroviral treatment (ART). Treatment with protease inhibitors (PIs) and, to a lesser extent, nucleoside analogue reverse transcriptase inhibitors (nRTIs) and non nucleoside reverse transcriptase inhibitors (NNRTIs) has been linked to hyperlipidemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, and increased insulin resistance [15]. Chronic HIV infection is also linked to low levels of total and high-density lipoprotein cholesterol (HDL-C) [16].

Even though studies on the effectiveness of lipid-lowering therapy in HIV-infected patients are limited, current HIV Medicine Association of the Infectious Disease Society of America (IDSA) and Adult AIDS Clinical Trial Group (AACTG) regulations support handling dyslipidemia in HIV-infected patients in the same way that it is managed in the general population, according to the NCEP Adult Treatment Panel III guidelines [17]. Knowledge of preexisting lipid abnormalities before starting ART, contributions of specific ART to lipid abnormalities, and pharmacological interactions between ART and lipid-lowering drugs are all important issues for HIV-infected patients [18].

Current Pharmacological Management for HAART-Associated Dyslipidemia

In HIV patients, dyslipidemia might be difficult to control. Weight loss and calorie restriction are always indicated as part of the treatment of this type of severe hyperlipidemia. As a result, lipid-lowering therapy may be necessary in the majority of HIV dyslipidemia patients. Statins' therapeutic advantages and safety in patients with a wide range of high CVD risks, as well as statins' safety as monotherapy or in combination with other lipid-lowering drugs, have been proven in recent big clinical trials [19].

A number of lipid-lowering treatments have been investigated in HIV infection. The treatment of dyslipidemia in HIV patients is complicated by the possibility of pharmacological interactions between ARV and lipid-lowering medicines. HIV-treatment drugs such macrolide antibiotics, azole antifungals, and rifamycin antimycobacterials may interact unfavorably with lipid-lowering therapies.

First line drug therapy

In HIV patients all over the world, statins are used to treat hyperlipidemia and cardiovascular diseases (CVD). In a collaborative meta-analysis of randomized clinical trials, statin therapy was linked to a slightly increased risk of developing diabetes, but the risk was low, both in absolute terms and when compared to the reduction in coronary events, and statins can be prescribed for people with moderate to high cardiovascular risk or existing CVD [20].

Currently, the first-line medications for dyslipidemia are HMG CoA reductase inhibitors (statins), which target LDL or Low-Density Lipoprotein Cholesterol, also known as Bad Cholesterol, and fabric acid derivatives (fibrates), which target triglycerides. Statins or fibrates, as well as a healthy lifestyle, can usually assist you control dyslipidemia. The important thing is to continue taking your meds as long as they are helping you manage your numbers and you are not experiencing any negative side effects. People who have reached their cholesterol objectives may be able to stop taking statins [21].

HMG-CoA reductase inhibitors are the medications of choice for most individuals with hypercholesterolemia because they lower LDL cholesterol the most effectively. For people with severe hypertriglyceridemia, gemfibrozil (Lopid) or nicotinic acid may be a preferable option. HMG-CoA reductase inhibitors (statins) include lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), atorvastatin (Lipitor), and cerivastatin (Baycol). To various degrees, all of these medicines lower total, LDL, and triglyceride cholesterol while somewhat raising the HDL percentage. Despite the fact that these medications are generally well tolerated, a small percentage of patients may develop increased hepatic transaminase levels, necessitating treatment discontinuation. Myopathy and gastrointestinal issues are two further negative effects [22].

Alternative therapy

Bile acid sequestrants and nicotinic acid (niacin) are examples of second-line agents in dyslipidemia management, not specifically for HAART-induced dyslipidemia. According to NCEP (National Cholesterol Education Program) guidelines, patients with a higher risk of CHD should undergo more intense dyslipidemia treatment than those with a lower risk. People with a history of CHD or extracoronary atherosclerosis are at the highest risk of having another heart attack or stroke. In all practical terms, patients with many risk factors for CHD but no prior history of the condition should be treated just as aggressively as those with the disease [23]. However, bile acid sequestrants are known to elevate TG levels, which might worsen a common lipid imbalance in HIV-infected individuals [24],and should be avoided because they have the potential to interfere with antiretroviral absorption[25].

Niacin, by decreasing VLDL cholesterol synthesis in the liver, increasing HDL cholesterol synthesis, suppressing lipolysis in adipose tissue, and enhancing lipase activity, decreases LDL cholesterol synthesis. This drug increases HDL levels by 15 to 35 percent, lowers total and LDL cholesterol by 10 to 25%, and reduces triglyceride levels by 20 to 50%. Side effects of niacin include flushing, pruritus, gastrointestinal discomfort, hyperuricemia, gout, increased liver function tests, and glucose intolerance. Flushing and pruritus, on the other hand, often go away on their own with sustained use. Niacin should be taken with meals to lessen the risk of gastrointestinal distress. Hepatotoxic side effects are more prevalent in sustained-release niacin preparations than in conventional formulations [26].

Because hypertriglyceridemia is widespread in HIV patients, and fibrates have low pharmacologic interactions with antiretrovirals, fibrates are an interesting treatment alternative in managing dyslipidemia. Fibrates lower triglycerides by 40-50 percent in HIV-infected patients with hypertriglyceridemia, with bigger reductions in those with higher baseline TG levels [27]. Additionally, fibrates may be the first-line treatment option for patients with hypertriglyceridemia (triglycerides greater than 500 mg/dL)[28]. These effects resemble those of statins, and in one research, they exceeded switching from PI to NNRTI. Fibrates appear to be well tolerated in studies, with the most prevalent side effect being gastrointestinal distress.

In HAART-induced dyslipidemia, ezetimibe, which blocks cholesterol absorption in the intestine and is metabolized independently of the CYP3A4 pathway, appears to have minor effects as monotherapy [29]. When combined with pravastatin, it allowed 62 percent of hyperlipidemia patients to achieve a target LDL-C concentration of 130 mg/dl [30]. In HAART-induced dyslipidemia, its effects appear to be limited to LDL-C lowering with little effects on triglycerides.

Due to the fact that they do not appear to be adversely affected by HIV infection or antiretroviral therapy, omega-3 fatty acids are also viable therapy alternatives, particularly in individuals with high triglycerides and low HDL lipid issues [28].

Combination therapy is also being used currently in the management of dyslipidemia in HIV patients. In an open label study, those who failed to satisfy NCEP recommendations on each drug as monotherapy for 12 weeks might add pravastatin or fenofibrate[31]. Despite the fact that combination medication was well tolerated and resulted in considerable TG reductions, only 4% of patients fulfilled the combined NCEP recommendations. Because statins and fibrates increase the risk of rhabdomyolysis in HIV-negative people, their use in HIV positive patients should be done with great caution. Despite preliminary indications that these novel drugs have a lesser impact on lipids, long-term safety data is needed, and doctors must be on the alert for treatment-related drug toxicity in order for HIV patients to live an extended life[32].

Possible Pharmacological Management for HAART-Associated Dyslipidemia

Alirocumab and Evolocumab

The European Medicines Agency has authorized two mAbs (alirocumab and evolocumab) for use in people with familial hypercholesterolemia, patients who failed to achieve satisfactory lipid management despite optimum lipid lowering treatment, and those intolerant to statins [33]. In a recently reported study, Evolocumab was found to be safe and effective in lowering lipid levels in dyslipidemic PLHIV on maximally tolerated statin treatment [34].
Evolocumab is an effective medication for decreasing atherogenic lipoproteins in people with HIV who are at high risk of cardiovascular disease [34]. Alirocumab is a monoclonal antibody that suppresses the proprotein convertase subtilisin-kexin type 9 (PCSK9) enzyme, and has been proven to lower LDL cholesterol levels in individuals on statin medication. To establish safety and efficacy, larger and longer-term trials are required[35].

Hormone Replacement Therapy (HRT)

Despite the fact that estrogen treatment has not been licensed for the use of dyslipidemia treatment, estrogen replacement therapy should be investigated as a means of decreasing LDL cholesterol and boosting High Density Lipoprotein cholesterol in postmenopausal women. A recent study shows that postmenopausal women who undergone postmenopausal HRT (Hormone replacement therapy) had a decreased mortality rate, albeit the benefits of extended use were seen to fade. Hormone replacement therapy can be taken with other cholesterol-inducing medications for the enhancement of lipid profile alterations. Pravastatin combined with conjugated estrogen has been proven to be more effective than either medication alone in lowering LDL cholesterol levels [36].

Leptin and Growth Hormone

Other experimental treatments include supplementing leptin to people who don't have enough of it, and giving them high levels of growth hormone[28]. Only HIV-infected people who are hypoleptinemic might benefit from recombinant leptin therapy research to treat metabolic syndrome. For people with HIV-related lipodystrophy and metabolic issues, recombinant human leptin, which is still being studied, is not yet commercially available. Due to a dearth of longer and larger well-equipped clinical research from various nations, the scope of its therapeutic utility is severely constrained [37].
Moreover, results of another trial showed that leptin was well tolerated, although it resulted in a loss of lean mass. Treatment with leptin was linked to a significant reduction in dyslipidemia. Insulin sensitivity in the liver improved, and lipolysis reduced. Visceral fat decreased, but peripheral lipoatrophy did not worsen. The findings of this pilot study suggest that leptin should be studied further in HIV-associated lipoatrophy patients [38]. These treatments were found to be effective in patients with HIV lipodystrophy, with improvements in visceral body fat, insulin resistance, and serum lipid profiles observed in both groups. Aside from the absence of severe or frequent adverse effects, there was no significant increase in glucose, HbA1c, or glucose intolerance levels during the study period [28].

Thiazoldinediones

Thiazolidinediones are PPAR agonists that improve insulin sensitivity by increasing glucose transport, peripheral glucose consumption, and adipocyte differentiation [39]. It has been shown to improve symptoms in ART patients [40-42] and to reduce limb fat mass in HIV-1/AR-associated lipodystrophy syndrome patients [41]. However, recent study reveals that thiazolidinediones do not protect against HAART-related lipodystrophy[43]. Furthermore, rosiglitazone has recently been linked to the occurrence of adverse cardiovascular events in diabetics, whilst pioglitazone has been found to interact with PIs via CYP3A4 suppression[44]. Taking this into account, it is probable that thiazolidinediones are not as effective as previously thought in the treatment of HAART-associated lipodystrophy. Furthermore, thiazolidinediones may be less effective in HIV patients on antiretroviral therapy (ART) than in the general population with metabolic syndrome, according to another study[28].

Acipimox

Acipimox, a drug with a long half-life and a structure comparable to niacin, has been linked to decreased insulin resistance and reduced TG levels in HIV-1 adult patients. In a double-blind research, cholestin was able to lower TC and LDL cholesterol levels without affecting HDL or TG levels, and without causing any side effects[45].
Acipimox resulted in significant sustained decreases in lipolysis, improved glucose homeostasis, and significant but moderate reductions in triglycerides in HIV-infected patients with aberrant fat distribution and hypertriglyceridemia. The improvement in acipimox's overall metabolic profile suggests that it may have therapeutic benefit, which needs further investigation [46].

Tesamorelin

Tesamorelin, a rhGH releasing hormone analogues, have been designed to increase GH pulsatility while maintaining negative feedback inhibition of insulin-like growth factor-1 [47]. Tesamorelin reduces visceral fat by 18% and helps HIV-infected people with central fat buildup feel better about themselves. These changes are made without causing any significant side effects or disrupting glucose levels [48]. In another study, tesamorelin medication was generally well tolerated and resulted in long-term reductions in VAT and triglycerides without increasing glucose levels after 52 weeks.

Although the VAT benefits last for 52 weeks, they do not last beyond the course of treatment [49]. Additionally, anti-tesamorelin antibodies have also been observed in individuals receiving tesamorelin medication, albeit the therapeutic ramifications of this are still unknown[47].

Problem with the Current Management

Drug-drug interactions between Antiretroviral therapy and lipid-lowering drugs

Choosing the lipid-lowering agent that is effective and safe to meet lipid goals at the same time, considering the drug-drug interactions between antiretroviral drugs is one of the most difficult aspects of treating dyslipidemia in HIV patients receiving antiretroviral therapy. The cytochrome P450 isoenzyme CYP3A4 is responsible for the metabolism of certain PIs, NNRTIs, and statins. When a PI combination of saquinavir/ritonavir is co-administered with simvastatin, the amount of simvastatin increases because of the inhibition of CYP3A4 by the PI combination [50]. To prevent the risk of patients developing rhabdomyolysis, the use of PIs is contraindicated with simvastatin [51]. Lovastatin is also indicated since it has a similar interaction with PIs. NNRTIs and statins have been known to interact in the past. Higher doses of statins are required together with the use of efavirenz. The drug is both an inducer and inhibitor of CYP3A4 which decreases pravastatin area under the curve (AUC) by 40%, atorvastatin AUC by 43%, and simvastatin AUC by 58%. A CCR5 receptor inhibitor, particularly Maraviroc, is a CYP3A substrate and may interact adversely with statins. Patients should be observed for any potential negative effects when lipid-lowering medications are given alongside antiretroviral drugs [52].

The risk of diabetes associated with statin administration

Statins are ubiquitous when it comes to the treatment of cardiovascular disease and cardiovascular risks such as dyslipidemia in HIV patients. According to a conclusion in a collaborative meta-analysis of randomized clinical trials, statin medication is related to a marginally higher risk of acquiring diabetes. Statins can be administered for those at mild to high risk of heart disease or for people who are already CVD patients since the risk was modest both in definite terms compared to the lowering in cardiovascular mortality [53]. Moreover, in a meta-analysis of five statin trials, intensive-dose therapy was linked with a higher risk of new-onset diabetes compared with moderate-dose statin therapy [54]. Over 161, 808 postmenopausal women aged 50 to 79, who all have statin medication use in common, appear to have an increased risk of diabetes [55]. It is indeed worth noting that continuing to observe blood glucose levels in HIV patients on statin medication is recommended in clinical practice. More research is needed to determine whether statin use in HIV patients increases the incidence of diabetes.

Genetics

Both before and after commencing ART, genetic variables have a key role in lipid variability among HIV-infected patients, accounting for a considerable fraction of the variation in lipids. Researchers examined the influence of 42 genetic polymorphisms and other important factors including antiretroviral treatment and HIV clinical characteristics on dyslipidemia in 745 Swiss HIV cohort participants. Single-nucleotide variants were shown to be responsible for 6% of the variance in HDLC, 7% in triglycerides, and 8% in non-HDL-C [56]. Antiretroviral therapy was responsible for a smaller proportion of the variation in these lipid markers. People with a higher dyslipidemic genetic profile on antiretroviral therapy had a three to a five-fold greater chance of persistent dyslipidemia compared to others with a lower dyslipidemic genetic profile [57].

Discussion

Receiving HAART was linked to significantly higher total cholesterol, LDL cholesterol, and triglycerides [58]. The standard practice is prevention by lifestyle and diet changes, followed by ART modification. Antihypertensive, antihyperlipidemic, and insulin sensitizers would generally be included in the regimen after that. Inclusion of a statin with the least risk for drug-drug interactions is the next step if the patient is already vulnerable to atherosclerosis or dyslipidemia and lipodystrophy manifestations[28].

Statin Therapy

Simvastatin and lovastatin

Statins are utilized in the treatment of hyperlipidemia and CVD in HIV patients all over the world [59]. In HIV patients on ART, simvastatin and lovastatin should be avoided [60], and it is especially contraindicated with HAART such as PI or delavirdine[61-67]. Multiple occurrences of rhabdomyolysis have been documented in individuals receiving different PI-containing ART after the addition of simvastatin[68-70]. Simvastatin should not be used in conjunction with ART because of inadequate evidence, substantial drug-drug interactions, and the availability of safer statins[60]. Concurrent use of lovastatin and PIs is contraindicated[71], but usage with NNRTIs may necessitate lovastatin dosage increases to achieve desirable lipid lowering effects[60]. Due to substantial medication interactions and a lack of clinical data, lovastatin should not be administered in ART patients[60].

Fluvastatin

Fluvastatin was recommended as an acceptable option to atorvastatin and pravastatin for patients using protease inhibitors by the HIV Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group [65, 72-73]. However in a different guideline, concomitant fluvastatin should be avoided due to the lack of evidence, decreased potential effectiveness when used with ritonavir, and cost-efficient convenience of safer statins [74]. Its use is also not recommended with nelfinavir [75].

Atorvastatin

A number of studies on atorvastatin medication in PLWH have been reported [76-79]. Concurrent use of atorvastatin with either PI- or NNRTI-based ART is considered safe. A panel of experts from the Adult AIDS Clinical Trial Group, HIV Medicine Association of the Infectious Disease Society of America, and the International AIDS Society USA endorsed atorvastatin as a first-line treatment for elevated LDL-C levels, starting at 10 mg once daily. Use with caution when taken with fenofibrate. In certain cases, atorvastatin (together with clarithromycin and lopinavir/ritonavir, delavirdine) was linked to rhabdomyolysis [80-82].

Pravastatin

Considered as the first-line treatment for HIV dyslipidemia is pravastatin[59]. Concomitant pravastatin use is considered safe in patients receiving either PI- or NNRTI-based ART. Higher starting doses of pravastatin may be considered in patients receiving NNRTI, particularly EFV or SQV-based ART, while the lowest pravastatin dose necessary should be used in ATV or DRV-based ART[25, 60]. Interestingly, fenofibrate and pravastatin combined therapy for HIV-related dyslipidemia improves lipid profiles significantly and appears to be safe. Pravastatin and atorvastatin were recommended as first-line agents by the International AIDS Society USA panel[83-85]. However, rhabdomyolysis has been reported with the combination of pravastatin/fenofibrate in a patient on a COBI-boosted PI regimen[86].

Rosuvastatin

In HIV patients using PI-based ART, DHHS guidelines urge that rosuvastatin should not be simultaneously used, given the reliability of other statins at moderate-intensity dosages [60]. The European AIDS Clinical Society (EACS), on the other hand, claims that rosuvastatin is generally safe when started at a low dose, increased to a maximum of 20 mg, [74] and closely observed for unwanted effects [60]. Interestingly, in HIV-1-infected patients taking a boosted protease inhibitor, rosuvastatin 10 mg/day was found to be more effective than pravastatin 40 mg/day in lowering LDL-C and triglyceride levels. Rosuvastatin and atorvastatin outperform pravastatin in terms of total cholesterol, LDL-C, and non-HDL-C reductions [78,87-88].

Non-statin lipid lowering therapies

Several additional drugs, including fibrates, ezetimibe, niacin, and omega-3 fatty acids, are approved for the treatment of dyslipidemia in HIV patients[89]. As monotherapy, ezetimibe is an effective and safe antihyperlipidemic medicine in HIV dyslipidemia, and it can also be prescribed in those who do not respond well to statins [29, 90-94]. It is also a safe addition to statin treatment for mild LDL lowering[89]. Furthermore, in individuals with HIV-associated dyslipidemia, a research indicated that the combination of ezetimibe and rosuvastatin improved TG, AIP, and non-HDL cholesterol levels more than a rosuvastatin dosage increase[95].

Fenofibrate is usually safe and effective medication used for the treatment of hypertriglyceridemia and mixed dyslipidemia in PLWH. Fish oil, niacin, and pravastatin in combination alongside fenofibrate are deemed safe and effective [31,96-103]. Another research found that individuals who completed fenofibrate and pravastatin combination medication had further improvements in lipid markers [31]. Fortunately, their metabolism does not rely on CYP3A4, therefore medication interactions are less common. Because of the lower likelihood of medication interactions with ART, fenofibrate and fenofibric acid are favored over gemfibrozil [89]. Co-treatment with fibrates and statins, on the other hand, carries the risk of hepatotoxicity [28].

Niacin was found to be helpful and safe in improving the lipid profile of HIV patients in two studies [104-106]. It is used when TG levels are high, but it should come only after fibrates and omega-3 fatty acids [89]. Also, because niacin can cause insulin resistance, it should only be used in pre-diabetic or diabetic patients [25].

Treatment with omega-3 fatty acid sources is typically well tolerated and has minimal side effects [107]. Furthermore, anti-inflammatory capabilities and absence of medication interactions with ART drugs are advantageous [25]. When TG levels exceed 500 mg/dL, omega-3 fatty acids should be considered, particularly in combination with fibrates for synergistic TG reduction [102].

Possible Treatments

The PCSK9 (proprotein convertase subtilisin/kexin type 9) genes generate instructions for the regulation of cholesterol levels in the bloodstream. Cholesterol (component of LDLC) is defined as a waxy, fat-like molecule produced by the body and taken from animal-derived foods. The PCSK9 protein also regulates the amount of low-density lipoprotein receptors (LDLRs), which are proteins found on the surface of the cell. These receptors are important in controlling blood cholesterol levels. Low-density lipoproteins (LDLs) are the principal carriers of cholesterol in the blood, and the receptors bind to them. The liver, which is responsible for eliminating the majority of excess cholesterol from the body, has a high concentration of low-density lipoprotein receptors [108]. Lipoprotein abnormalities have been reported frequently after starting HAART. The regulation of hepatic LDL receptor expression is a major mechanism by which plasma LDL cholesterol levels can be influenced via the regulation of hepatic LDL receptor expression. Medications such as Alirocumab and evolocumab were used to treat patients with primary hypercholesterolaemia or mixed dyslipidemia[109]. Alirocumab and evolocumab are fully humanized monoclonal antibodies that bind free plasma PCSK9, promoting degradation of PCSK9 enzymes. As a result, less free PCSK9 is available in plasma to bind to LDL receptors (LDLRs). This results in a higher fraction of LDL receptor (LDLR) recycling towards the hepatocyte surface[110]. Evolocumab inhibits PCSK9 protein and prevents it from binding to the LDLR, allowing LDLR to recycle back to the liver. By inhibiting the protein, the drug increases the number of LDLRs to clear from the blood, reducing LDL levels [111].

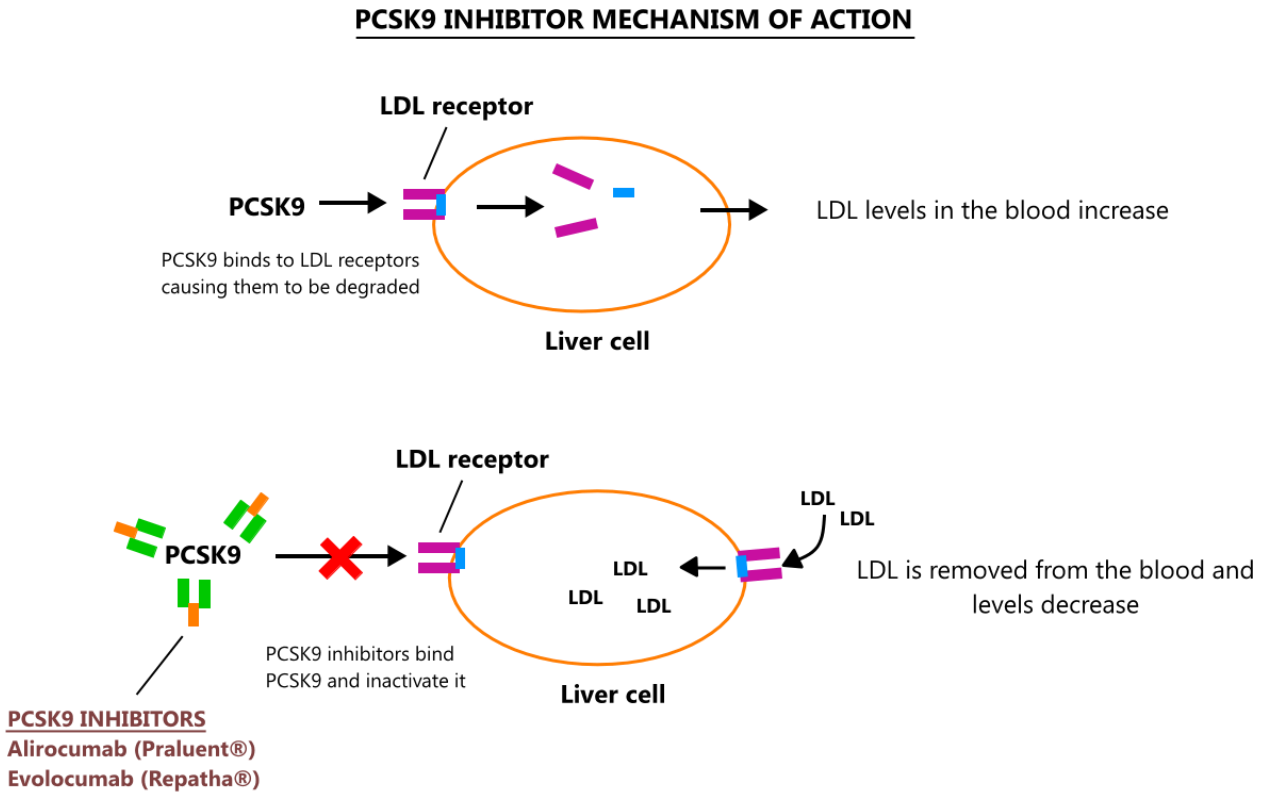

Figure 1. Illustration showing PCSK9 Inhibitor Mechanism of Action

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; LDL, low-density lipoprotein

Source: https://www.straighthealthcare.com/pcsk9-inhibitor-moa.html

Alirocumab has more indications than evolocumab in patients with high CV risk who aren't meeting their LDL Cholesterol (LDLC) target goals, while evolocumab has more evidence in patients with heterogeneous familial hypercholesterolemia and patients with varying CV risk who aren't meeting their LDLC target goals [112].

In the treatment of LDLC lowering therapy with alirocumab or evolocumab on individuals, clinical efficacy and safety still remains undetermined. A study was conducted to evaluate the efficacy and safety of alirocumab and evolocumab in patients with dyslipidemia or atherosclerotic cardiovascular disease. Overall, the effects of PCSK9 inhibition on all-cause death and cardiovascular death were not statistically significant. Proprotein convertase subtilisin-kexin type 9 inhibitors were associated with lower risk of MI, ischaemic stroke, and coronary revascularization, compared with the control group. Use of these PCSK9 inhibitors was not associated with increased risk of neurocognitive adverse events, liver enzyme elevations, rhabdomyolysis, or new-onset diabetes mellitus.

Following the study results, alirocumab or evolocumab inhibition of PCSK9 was linked to a lower risk of MI, stroke, and coronary revascularization, with a favorable safety profile for both medications (alirocumab or evolocumab) [113].

There are people that while being on HAART/ART, undergo hormone replacement therapy (HRT), doubting if there are interactions between those medications. However, the Centers for Disease Control and Prevention (CDC) Trusted Source states that there are no known drug interactions between HAART/ART and hormone replacement therapy (HRT). In a 2020 study determining the interactions between HAART/ART and transgender hormone

replacement therapy, there were no changes found in the effectiveness of hormone treatment after 4 weeks of HIV treatment. The participants had no changes in their HRT dosing and there were no signs of HRT withdrawals while on HAART/ART. However, there are possible drug interactions, such as whether an HAART/ART drug will increase the risk of someone on hormone replacement therapy related issues. Doctors will determine these risks in each case as they redefine the patient's treatment regime [114].

Alirocumab and Evolocumab are promising given that their uses were approved by the European Medicines Agency [33]. Evolocumab was shown to be safe and effective in PLWH, however studies are needed for the concomitant use of alirocumab with HAART. Hormone replace therapy (HRT) has also shown its promising value especially in postmenopausal women [36], but its concomitant use with HAART should also be investigated.

Presently, no medication approval or large-scale studies have been conducted for leptin and growth hormone, however they do offer promise as prospective treatment approaches for HIV-associated lipid disorders[31]. A study demonstrated in its proof-of-concept experiment that treatment with recombinant human leptin improves insulin resistance, reduces hyperlipidemia, and decreases central fat mass in people with HAART-induced metabolic syndrome and hypoleptinemia within two months. These findings were supported by a six-month independent research. Further clinical trials will be conducted for the safety and efficacy of human recombinant leptin alone or combined with thiazolidinediones for PLWH [115].

Lipoatrophy and insulin resistance are metabolic drawbacks associated with highly active antiretroviral therapy (HAART). Although there is currently no evidence to support the use of thiazolidinediones in the treatment of HAART-related lipoatrophy, treatment of lipoatrophy-related diabetes may be guaranteed. Thiazolidinediones should be examined in these patients for novel indications such as hepatosteatosis[116]. Thiazoldinedione was given great value as a potential therapy for HAART-induced dyslipidemia. However, reports from several trials show that it is not as significant and beneficial as the treatments currently given, ruling out its use in HIV patients on ART.

Tesamorelin, a GHRH analogue, has been approved by the FDA to reduce excess visceral fat accumulation in HIV lipodystrophy [117]. Research also shows that acipimox could be a good alternative to other lipid-lowering drugs that do not have as many side effects and counter interactions [118]. Usage of tesamorelin and acipimox exhibits favorable safety, efficacy, and tolerability thus warrants for more thorough investigations on their use on HAART-induced dyslipidemia.

Conclusion

The human immunodeficiency virus has become a chronicaly controllable disease, and one of the elements that must be handled in order to maintain quality of life and lifespan is the cardiovascular risk. [25]. One of the most prevalent risk factors that may be addressed is dyslipidemia. Effective dyslipidemia therapy might be difficult because of several drug–drug interactions between various ART drugs and lipid-lowering medications. Several commonly used lipid-lowering medications have proven their worth as the current management regimen. These include several statins, fibrates, niacin, ezetimibe, and combinations of fish oil. These drugs are studied in PLWH and are shown to be successful in lowering bad cholesterol [22].

To prevent dangerous drug-drug interactions in patients undergoing ART, careful lipid-lowering medication selection is essential. Clinicians must be knowledgeable about the complexities of statin selection for the prevention of CVD in HIV patients under antiretroviral treatment. Tailor-fitting lipid medication for each patient and starting at the lowest viable statin dose are recommended practices in terms of managing dyslipidemia in HIV patients [54].

Even so, these current management poses risks in the long run and they should still be monitored for any potential toxicities [80]. With this, other possible medications have shown their promising potential. These include alirocumab, evolocumab, hormone replacement therapy, leptin, growth hormone, acipimox, and tesamorelin. Due to the lack of studies, they lack worldwide approval for the treatment of dyslipidemia. Therefore, further clinical trials are needed to explore better HAART-induced dyslipidemia management options to ensure that optimal therapy is given to people living with HIV.

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