Review

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Abstract: Infection with human immunodeficiency virus (HIV) and induced acquired immune deficiency syndrome (AIDS) represent one of the greatest health burdens worldwide. The complex pathophysiological pathways that link highly active antiretroviral therapy (HAART) and HIV infection *per se* with dyslipidemia make the management of lipid disorders and the subsequent increase in cardiovascular risk essential for the treatment of people living with HIV (PLHIV). Amongst the HAART regimens, darunavir and atazanavir in terms of protease inhibitors, tenofovir disoproxil fumarate, nevirapine or rilpivirine in terms of nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors respectively, and especially integrase inhibitors, have demonstrated the most favorable lipid profile emerging as sustainable options in HAART substitution. To this day, statins remain the cornerstone pharmacotherapy for dyslipidemia in PLHIV, although important drug-drug interactions with different HAART agents should be taken into account upon treatment initiation. For those intolerant or not meeting therapeutic goals, the addition of ezetimibe, PCSK9, bempedoic acid, fibrates or fish oils should also be considered. This review summarizes the current literature on the multifactorial etiology and intricate pathophysiology of hyperlipidemia in PLHIV, with an emphasis on the role of different HAART agents, while also providing valuable insights into potential switching strategies and therapeutic options.

Keywords: HIV; dyslipidemia; metabolic syndrome; antiretroviral therapy; switching strategy

1. Introduction

Since the first case reports in 1981, human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) remain among the world's greatest pandemics, with more than

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39 million people living with HIV (PLHIV) and 1.3 million newly infected in 2022.[1] The development of highly active antiretroviral therapy (HAART) has transformed AIDS into a rather long-term chronic condition through substantial suppression of viral load, partial restoration of the immune system, and decreased fatal HIV-related illnesses.[2,3] With nearly normal life expectancy among PLHIV who receive HAART, it is estimated that 73% of HIV-infected individuals will be over 50 years old by 2030, highlighting age-related comorbidities such as metabolic syndrome (MetS) and the consequent cardiovascular disease (CVD), as an emerging problem. [4–6] MetS, characterized by abdominal obesity, high blood pressure, increased fasting glucose, increased triglycerides (TGs) and decreased high-density lipoproteins (HDLs), is highly associated with CVD.[7,8] Its prevalence ranges between 11% and 48% among PLHIV, and it is estimated that 78% of them will develop CVD at some point in life.[6,9] Moreover, individuals with HIV receiving HAART face greater risk for major metabolic-related cardiovascular events as compared with those uninfected, experiencing earlier manifestations of heart failure, while also demonstrating nearly a two-fold increased risk for myocardial infarction and a four-fold increased risk for sudden cardiac death.[10–14]

Dyslipidemia, a cornerstone of MetS and a well-established risk factor for CVD, is responsible for roughly 50% of all cardiovascular events among PLHIV. Lipid abnormalities that include low levels of HDL, low-density lipoprotein (LDL), total cholesterol (TC), elevated TG and oxidized LDL (oxLDL) lead to an atherogenic profile in more than 67% of women and 81% of men with HIV infection.[15–18] In more detail, the underlying mechanisms of dyslipidemia in PLHIV involve complex pathophysiological pathways associated with, in addition to traditional risk factors, both HAART treatment and HIV infection per se. HIV encoded proteins modify the expression of regulatory genes and the function of cell membrane proteins, resulting in the accumulation of free fatty acids (FFAs) leading to lipotoxicity, while chronic inflammation and immune activation seen in HIV infection lead to increased levels of cytokines, decreased TG clearance, increased levels of oxLDL, as well as alterations in lipid particle composition.[19–23] Moreover, as adipose tissue serves as a reservoir for HIV, inflammation plays a key role via a continuous interplay between CD4+ T cells, macrophages and adipocytes, further dysregulating lipid metabolism, specific HAART categories are implicated in the redistribution of adipose tissue in the form of lipodystrophy.[24–28] Besides the aforementioned frequent clinical entity in PLHIV, antiretroviral treatment can even promote dyslipidemia with numerous molecular mechanisms, with some protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), having the most profound effects on lipidemic profile.[29,30] Severe drug-drug interactions between HAART and statins, combined with limited evidence of newly-introduced hypolipidemic agents in HIV population, bring to the surface the importance of switching from older HAART regimens to lipid-friendly ones, highlighting that the management of dyslipidemia in PLHIV is a rather demanding issue.

The purpose of the present review is to summarize the current literature on the multifactorial etiology and intricate pathophysiology of hyperlipidemia in PLHIV, focusing on the role of different HAART agents, while also providing valuable insights into possible switching strategies and treatment options.

2. The Molecular Mechanisms of HIV-Associated Dyslipidemia

2.1. The Role of HIV Viremia

HIV infection induces lipid abnormalities via several mechanisms, with the shedding of viral proteins, immunological activation, and persistent inflammation prevailing among them. Vpr, an HIV protein responsible for viral replication that plays a multifactorial role by inhibiting the peroxisome proliferator-activating receptor-γ (PPARγ) and stimulating the glucocorticoid receptor (GR) and the liver X receptor-a (LXR-α), leads to preadipocyte differentiation, dysregulation and overaccumulation of FFA, while it also decreases hepatic fatty acid oxidation and reduces hepatic VLDL-TG exportation, ultimately leading to lipodystrophy.[31–35] Tat, a regulatory HIV protein involved in viral transcription, also interferes with normal cholesterol turnover and esterification through upregulation of genes encoding genes encoding 7-dehydrocholesterol reductase (DHCR7), resulting in increased levels of free cholesterol, TC, and cholesteryl esters.[20,36,37] Furthermore, Tat

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induces the expression of adhesion molecules and stimulates monocyte chemoattractant protein-1 (MCP-1)-mediated monocyte transmigration, perpetuating immune activation and inflammation.[38,39] Another protein shed by HIV, Nef, holds an important role in viral replication and immunological escape of HIV, while also exhibiting a bifactorial role in cholesterol bioavailability. It stimulates cholesterol biosynthesis and inhibits its efflux by suppressing the activity of the ATP-binding cassette transporter protein A1 (ABCA1), while at the same time disrupting caveolin-dependent cholesterol transport in infected macrophages, resulting in decreased HDL levels and an abundance of lipid rafts. It also reduces endothelial nitric oxide (NO) production, increases inflammatory cytokine release, such as IL-6 and TNF-a, and promotes the secretion of MCP-1 from endothelial cells, inducing endothelial apoptosis, and promoting atherosclerotic plaque rupture and the development of acute thrombus.[23,40–45]

Inflammation plays a crucial role in dyslipidemia and associated atherosclerosis, serving both as a cause and as a consequence. In HIV infection, the subpopulation of CD14 + / CD16 + pro-inflammatory monocytes predominates, as indicated by the increased ratio of CD4 + / CD8 +, expressing activation markers and molecules presenting antigens such as CD38, CD69, CD11b, and CD86, resulting in tissue migration and turnover to cholesterol-pumped macrophages. These so-called foam cells found in adipose tissue together with activated CD4 and CD8 T cells, NK and NKT cells, result in the production of inflammatory mediators such chemokines CCL2, CCL5 and CX3CL1, c-reactive protein (CRP), IL-6, IL-8, IL-1β, IL-18, IL-2, IFNγ, IL-17A and TNF-Z, altering adipose cell function, impairing reverse cholesterol transport, and reducing HDL and apolipoprotein A-I (apoA-I) particle numbers.[46–51] Furthermore, these foam cells are highly concentrated in NADPH oxidases, enzymes that under a hyperlipidemic environment, up-regulate and form oxLDL, inducing endoplasmic reticulum (ER) stress and the production of reactive oxygen species (ROS), exacerbating both inflammation and foam cell formation, which are strong promoters of atherogenesis.[52–54] Along the same line, another mechanism which promotes the ongoing inflammation in HIV-associated dyslipidemia is the activation of NLRP3 inflammasome. In fact, once pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) recognize HIV particles through toll-like receptors (TLRs), the formation of an inflammasome occurs, resulting in a cascade of cytokines and the further production of IL-1β and IL-18.[55,56] Additionally, HIV infection is characterized by the production of interferon-alpha (IFN-a) as an attempt of the immune system to prevent viral entry and inhibit viral replication. Both IFN-a and TNF-a are associated with impaired oxidation of plasma FFAs, contributing to enhanced hepatic re-esterification and elevated plasma levels of TGs. Another important branch of inflammation-induced dyslipidemia is the alteration of the gut microbiome that occurs in HIV infection. In fact, damage to the intestinal epithelium, microbial translocation and subsequent production of microbial metabolites and toxins such as lipopolysaccharide, along with the downregulation of normal flora bioproducts such as butyrate, contributes to persistent inflammation, as measured by circulating soluble CD14 (sCD14), soluble CD163 (sCD163) and CRP, leading to increased TG/HDL ratio.[57–61]

2.2. The Role of Antiretroviral Treatment

The introduction of HAART as a combination of three antiretroviral agents, typically including two NRTIs and one PI, NNRTI or integrase strand transfer inhibitor (INSTI), has revolutionized the treatment of HIV infection. However, nowadays, the long-term metabolic side effects of those regimens, such as dyslipidemia, have become a concern.[62] The impact of HAART on the lipid profile is often challenging to determine, considering the significant variability between different classes of ART drugs and drugs within the same class, as well as the multidrug nature of HIV treatment itself. However, altered lipid parameters in HAART-experienced patients as expressed by high levels of TG, LDL and apolipoprotein C-III, persisting even 3 years after the initiation of HAART, have raised questions about the underlying etiology.[63,64] Furthermore, studies from the pediatric population that demonstrated a prevalence of dyslipidemia of up to 70% after 6-150 months of treatment, and studies that showed a nearly 15% increase in the prevalence of dyslipidemia and a significantly higher TG/HDL ratio 6 months after the initiation of HAART, highlight the eminent need of pathophysiological interpretation, especially in individuals with multi-drug resistant HIV.[65–67] The main reason behind the ongoing lipid dysregulation lies in the combination of continuous inflammation and immune activation, as HAART achieves viral suppression but not

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elimination, mitochondrial dysfunction and altered distribution of adipose tissue. In fact, adipose tissue and lipodystrophy syndrome, which manifests as lipohypertrophy with abdominal and dorsocervical fat accumulation or lipoatrophy with subcutaneous fat loss, holds a crucial role in dyslipidemia.[68] (Figure 1)

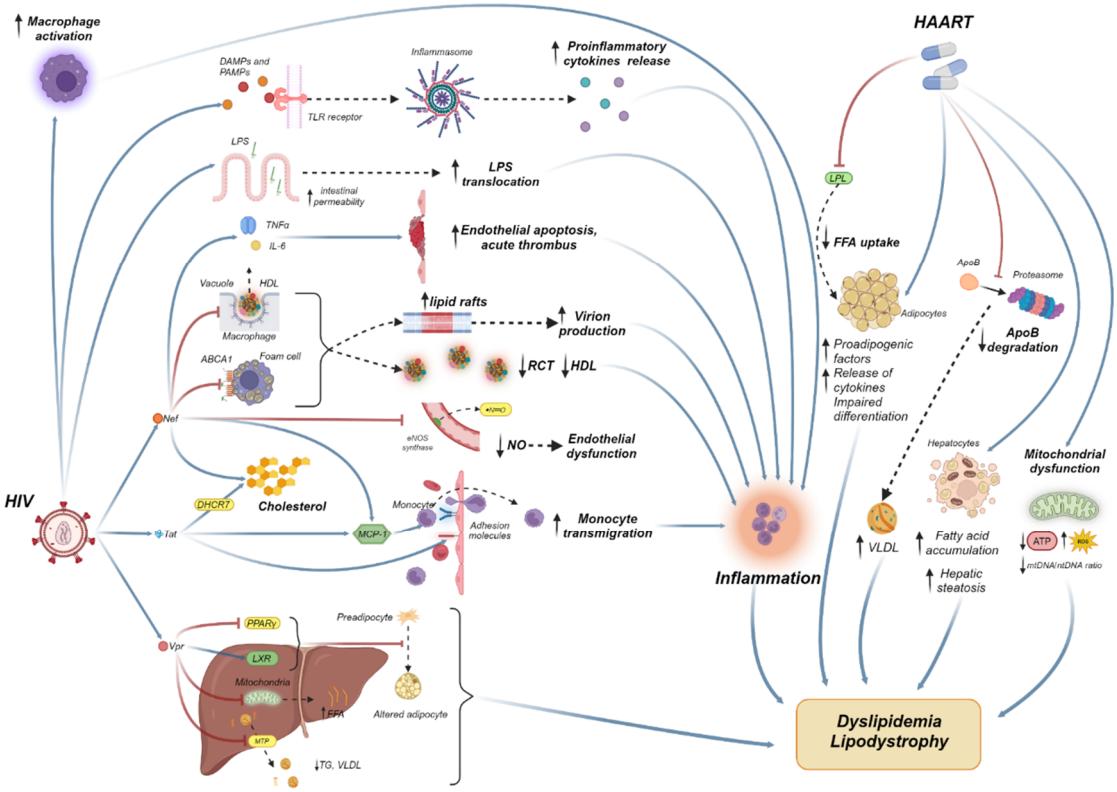

Figure 1. The pathogenesis of dyslipidemia in PLHIV under HAART. HIV induces macrophage activation, triggering an inflammatory response with the subsequent release of proinflammatory cytokines in various organs. In the arterial vessel wall, it leads to endothelial cell dysfunction, oxidation of LDL, and to the formation of atheromatous plaque. Additionally, HIV directly contributes to dyslipidemia by increasing the levels of FFA and VLDL, while also decreasing the functionality of HDL and impeding reverse cholesterol transport. Furthermore, the use of HAART exacerbates and intensifies dyslipidemia by inducing liver steatosis, promoting the accumulation of fatty acids, and fostering lipogenesis, causing abnormalities in adipocyte metabolism, leading to lipodystrophy. HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; DAMP: damage-associated molecular pattern; PAMP: pathogen-associated molecular pattern; LPS: lipopolysaccharides TG: triglyceride; VLDL: very low density lipoprotein; HLD: high density lipoprotein; LDL: low density lipoprotein; RCT: reverse cholesterol transport; NO: nitric oxide; FFA: free fatty acid; TNF-a: tumor-necrosis factor-a; PPARγ: peroxisome proliferator-activated receptor γ; MTP: microsomal triglyceride transfer protein; LXR: liver X receptors; IL: interleukin; MCP: monocyte chemoattractant protein; ATP: adenosine triphosphate; LPL: lipoprotein lipase; APO: apolipoprotein; TLR: toll-like receptor; ABCA1: adenosine triphosphate-binding cassette transporter A1.

2.2.1. Protease Inhibitors

PIs are mostly associated with lipohypertrophy and have numerous effects on lipid levels, with a substantial elevation in TG and VLDL levels, especially ritonavir (RTV), lopinavir (LPV) and saquinavir (SQV), and little to no effect on LDL and HDL levels, especially between generally lipid friendly darunavir (DRV) and atazanavir.[69,70] In general, PI-based regimens have a trend to develop greater atherosclerosis compared to non-PI-based regimens, as demonstrated by the increase in the intima media thickness (IMT), and the development of atheromatous plaques. More specifically, PIs inhibit lipolysis by altering lipoprotein lipase (LPL) activity, resulting in reduced TG uptake in adipocytes and elevated plasma TG levels.[71,72] Furthermore, they inhibit the nuclear localization

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of sterol response element binding protein-1 (SREBP-1) in adipocytes, resulting in downregulation of PPARγ, impaired adipocyte differentiation and insufficient lipid removal from circulation, while concomitantly promote nuclear localization of SREBP-1 in hepatocytes, resulting in excessive fatty acids synthesis.[73,74] Furthermore, inhibition of proteasomal apolipoprotein B (apoB) degradation and increased ER stress have been observed in cultures of hepatocytes and rat hepatocytes, respectively, resulting in increased VLDL and lipodystrophy.[75–77]

In the cross-sectional study D: A: D with 17,852 participants, individuals who received PI regimens were associated with higher levels of TC and TG than HAART-naive patients, while those receiving the dual-PI regimen had higher levels of both TG, TC, LDL and the TC / HDL ratio.[78] In a within-class comparison of RTV-containing regimens were associated with higher levels of TC and TG and TC/HDL ratio than indinavir (IDV)-containing regimens, while nelfinavir (NFV)-containing and SQV-containing regimens, were associated with a reduced risk of lower HDL levels and a lower TC / HDL ratio, respectively.[79] As implied, RTV demonstrated the most significant effect on lipid parameters, even 1 week after initiation of treatment, as indicated by the elevation of 146% TG level and the increase of 159% VLDL level, even in healthy normal individuals.[80,81] Interestingly, its lipidemic effect appeared to be dose dependent, given the fact that combined with other PIs, a low-booster dose resulted in increased TG and LDL levels by 26% and 16% respectively, while in full-dose, TGs increased by 83%, FFAs by 30% and VLDL by 33%.[82,83] In RTV-boosted LPV (LPV/r) regimens a further 28% to 108% increase in fasting and non-fasting TG levels was observed, which, combined with an increase of 25% in LDL levels and a concomitant reduced size of LDL particles, could be associated with high atherogenicity.[84,85] Although some studies demonstrated pretreatment baseline lipid values and LPV plasma concentration levels as important risk factors for induced hyperlipidemia, other studies did not verify this observation.[86–88] It is also worth mentioning that Amprenavir (APV) and NFV increased TG and LDL levels to a lesser extent than RTV or LPV/r, in HIV infected patients.[89,90] Moreover, ATV is considered to be among the most lipid-friendly PIs and has shown favorable lipid outcomes. In fact, some studies demonstrated the absence of a harmful effect on TG levels after 48 weeks of administration, even at a dose of up to 500 mg, while some others showed a significant decrease of 46% in TG levels with a concomitant improvement of 18% in TC levels, during the first 24 weeks after switching to the atazanavir-based regimen.[91,92] Newer PIs such as DRV share the beneficial effect of ATV on hyperlipidemia. Data from the ARTEMIS study that included 689 patients showed that DRV had smaller median increases in TG and TC levels, +1.8 mg/dl and +10.8 mg/dl respectively, compared to LPV, 10.8 and 16.2 mg/dl respectively, although in POWER studies enrolling heavily pretreated patients, a 15% increase in TG levels was observed.[93,94] Along the same line, in a phase 4, randomized exploratory study, DRV demonstrated an increase in apoA-I and consequently favorable changes in HDL levels, especially in HIV individuals with low CD4+ cell count, compared to ATV. [95]

2.2.2. Nucleoside Reverse Transcriptase Inhibitors

NRTIs, especially the thymidine analogues stavudine (d4T) and zidovudine (ZDV), have been implicated with dyslipidemia, mainly with adipose tissue alteration and induced lipoatrophy.[96] The main pathophysiological mechanism involved is mitochondrial dysfunction and cell toxicity through inhibition of DNA polymerase gamma and oxidative phosphorylation, increasing mitochondrial ROS production.[97,98] Increased incorporation and ineffective exonuclease removal of highly toxic dideoxy NRTI compounds, is presumably another important branch of mitochondrial dysregulation, while insufficient respiratory chain activity and ATP synthesis as an index of mitochondrial dysfunction, have been reported in lipodystrophic patients receiving NRTIs.[99–101] Especially ZDV has been associated with inhibition of mitochondrial adenylate kinase, adenosine nucleotide translocator, and electron transport chain, promoting ROS production.[102,103] Highlighting the great influence of NRTIs in adipose tissue, the expression levels of significant adipogenic factors such as PPAR-γ, SREBP-1, CCAAT / enhancer-binding protein alpha (C/EBP-α), adiponectin and leptin were abnormally low, while cytokine levels of IL-6 and TNF-α, being produced by stressed adipocytes and immune cells, were notably high. Furthermore, NRTIs were associated with depleted cellular mitochondrial DNA (mtDNA) and mitochondrial proliferation in adipocytes, as quantified by cellular mtDNA copy number and mitochondrial mass measurements, findings highly suggestive of lipoatrophy.[104] Similar findings with nearly 68% reduction in

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mtDNA/nuclear DNA levels were observed in peripheral blood mononucleated cells of HIV individuals treated with NRTIs, while significant inhibition of mitochondrial gene expression was demonstrated after a 2-week NRTI-based regimen even in HIV-negative patients.[104,105] Interestingly, some studies link these effects with lamivudine (3TC) to a lesser extent, compared to didanosine and d4T.[106]

A prospective multicenter study that enroled 873 HIV individuals who switched from d4T to tenofovir (TDF), demonstrated a sustained reduction in median levels of TC (-17.5 mg/dl), LDL (-8.1 mg/dl) and TG (-35 mg/dl) levels, with the greatest reduction observed among those with higher baseline values.[107] In fact, even a lower dose of d4T (30 mg bid instead of 40 mg b.i.d), showed a clinically significant improvement of lipid parameters in HIV treated patients.[108] Similar findings have been recorded with ZDV, which was associated with higher levels of TC and LDL compared to other first-line agents in China, suggesting a preemptive switch from thymidine analogues to other regimens to prevent further progression of dyslipidemia and lipoatrophy.[109,110] Furthermore, Abacavir (ABC) could be an alternative option of d4T and ZDV, as it has shown a positive effect in increasing limp fat and partially resolving lipoatrophy, even though an unfavorable lipid outcome has been observed, with higher levels of TG (25 mg/dl versus 3 mg/dl) and TC (34 mg/dl versus 26 mg/dl), as compared with TDF at 48 weeks, according to results from the ACTG 5202 study.[111,112] However, the increased overall cardiovascular risk associated with ABC limits the benefits of potential switching to ABC-based regimens.[113] 3TC, TDF and the newer agent tenofovir alafenamide (TAF), are the NRTI representatives exhibiting the most lipid-friendly profile, outmatching the rest of NRTIs in all lipid outcomes such as TG, TC, LDL and HDL levels.[70] Notably, a recent prospective cohort study of 1446 HIV individuals who switched from TDF to TAF had a mean weight increase of +0.5 kg at 144 weeks, and a significant increase in TC (+7.9 mg/dL) and TG (+11.2 mg/dL), with no differences in the TC/HDL ratio.[114] In addition, another recent observational, single-center study with 61 HIV individuals who switched from TDF to TAF, demonstrated a significant increase in TC 178 ± 38 to 194 ± 40 mg/dl, LDL levels 117 ± 32 to 137 ± 36 mg/dl, and average weight, but also an increase in HDL levels 45 ± 12 to 48 ± 13 mg/dl, indicating that despite the overall superiority of TAF in terms of stability and bioavailability, a personalized therapeutic approach regarding the metabolic risk should be taken into account.[115]

2.2.3. Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs have also shown an effect in dyslipidemia with increased TC, LDL, and TG levels and increased HDL levels, thus counterbalancing the overall lipid risk profile due to mitochondrial dysfunction, as established by detecting increased mitochondrial mass and decreased mitochondrial membrane potential.[116–118] Especially efavirenz (EFV) has been associated with increased ROS production and reduced ATP synthesis through inhibition of complex I, combined with induced hepatic cell apoptosis through modified cytochrome c and caspase 9 activity.[101,119] Furthermore, EFV can serve as a potent pregnane X receptor (PXR) selective agonist, inducing target gene expression such as the fatty acid transporter CD36 gene, resulting in increased lipid uptake and cholesterol biosynthesis in cells.[120] Indeed, the unfavorable lipid effect of NNRTIs, especially EFV, has been demonstrated in a 6-year prospective observational study of 433 immunosuppressed HIV individuals, which demonstrated high TC and TG levels, as well as increased TC and LDL levels as compared with ATV/ritonavir (ATV/r) treatment.[121,122] On the contrary, some other studies demonstrated favorable HDL and apoA-I levels of EFV as compared with ATV/r, as well as the superiority of EFV as compared with LPV in terms of TG levels.[123,124] Additionally, in a between-class comparison, the 2NN study evaluated the different lipid effects of 2 NNRTIs, EFV and nevirapine (NVP), in combination with 2 NRTI (d4T and 3TC), and showed a greater increase in TG, TC and LDL levels in the EFV arm, as compared with the NVP arm. Similar data have been extracted from the SCOLTA study enrolling 490 HIV individuals, within which switching from EFV to rilpivirine (RPV), another NNRTI, demonstrated a statistically significant improvement in TC, TG and LDL levels, and increased TC/HDL ratio in 12 months.[125] Finally, an interesting study of 50 HIV individuals that switched from a lipid-friendly NNRTI (NVP) to another lipid-friendly NNRTI (RPV), showed a significant reduction at week 24 of mean TC (-12 mg/dl), LDL (-6,5 mg/dl) and HDL levels (-5 mg/dl), with TG levels remaining rather stable, highlighting the challenging nature of HAART switching.[126]

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2.2.4. Integrase Inhibitors

INSTIs seem to exert minimal or negligible influence on lipid levels, even after long-term use, highlighting the beneficial role of these agents in dyslipidemia after switching from other HAART regimens, as suggested by current guidelines.[127] A recent meta-analysis of randomized controlled trials comparing integrase inhibitors with other antiretroviral classes (EFV-based or PI-based therapies) in naïve HIV patients, demonstrated that INSTIs led to decreased TC (MD -13.44 mg/dL), LDL (MD -1.37 mg/dL), HDL (MD -5.03 mg/dL), and TG levels (MD -20.70 mg/dL). However, a well-established risk of considerable weight gain among HIV individuals has been associated with INSTI-based treatment, compared to PIs and NNRTIs.[128–130] The pathophysiological pathway behind the aforementioned outcome is yet to be established, however, low CD4 count, high viral load and substantial weight loss before the initiation of HAART were associated with greater weight gain, implying that superior immune reconstitution in individuals with more advanced HIV infection appears to be independent risk factors for INSTI-induced fat accumulation.[132] Recent studies have demonstrated that dolutegravir (DTG) and, to a lesser extent Raltegravir (RAL), are associated with activation of lipogenic and adipogenic pathways, increased lipid accumulation, induced mitochondrial dysfunction and oxidative stress, low leptin and adiponectin secretion, and elevated periadipocyte fibrosis.[133,134] However, these adipose tissue alterations do not reflect unfavorable lipid outcomes, rather than insulin resistance.[135] Indeed, in the ACTG A5260s study, ART-naive patients undergoing RAL treatment, presented with a rapid two-fold increase in insulin resistance, similar to that observed with ATV/r and DRV/r, but on the contrary, another prospective randomized study, highlighted the superiority of RAL in all fasting lipid measurements including TC, TG, non-HDL and LDL, as compared with the two ritonavir-boosted PIs.[136,137] Furthermore, a Greek cohort study by Pantazis et al., demonstrated that INSTIs, especially DTG and RAL, as compared with Elvitegravir (EVG), led to faster and more profound weight gain in comparison with PIs and NNRTIs, with mean expected weight gain of 6kg in INSTI-based regimen group, while a cohort study of RESPOND study group with 4577 HIV individuals, demonstrated that elvitegravir/cobicistat (ELG/c) and RAL, were associated with higher incidence of dyslipidemia, as compared with DTG.[138,139] Apart from DTG, second generation INSTIs such as bictegravir (BIC), share the same lipid-friendly profile although significant weight gain has been recorded, with a study comparing DTG +3TC to BIC/FTC/TAF, demonstrating a significant decrease in TG levels (MC -14 mg/dL), and increased HDL levels (MC +3 mg/dL) in the DTG group, with a significant decrease in LDL levels (-13 mg/dL) in the BIC group.[140] Finally, another second generation INSTI, cabotegravir (CAB) in combination with RPV, had a promising lipid effect with a significant increase in HDL levels, a decrease in TC/HDL ratio, but little to no effect in LDL levels, regardless of the regimen prior to switching.[141] (Table 1)

Table 1. Summary of the effect of individual antiretroviral drugs on lipid parameters.

Drug class	Antiretroviral drug	Total Cholesterol	LDL-C	HDL-C	Triglycerides
Protease Inhibitors (PIs)	Atazanavir/Ritonavir	↔	↑	↔	↑
	Darunavir/Ritonavir	↔	↑	↔	↑
	Indinavir	↑	↑	↑	↑
	Lopinavir/Ritonavir	↑ ↑	↑	↔	↑ ↑
	Nelfinavir	↑	↑ ↑	↔	↑
Nucleotide reverse transcriptase inhibitors (NRTIs)	Abacavir	↑	↑	↔	↑
	Zidovudine	↑	↑	↔	↑
	Emtricitabine	↔	↔	↔	↔
	Lamivudine	↔	↔	↔	↔
	Stravudine	↑	↑	↓	↑
	Tenofovir	↔	↑	↑	↑
	alafenamide	↓	↔	↓	↔

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	Tenofovir disoproxil				
Non-nucleotide reverse transcriptase inhibitors (NNRTIs)	Efavirenz	↑	↑	↑	↑
	Etravirine	↔	↔	↔	↔
	Nevirapine	↑	↑	↑ ↑	↑
	Rilpivirine	↑	↑	↔	↔
Integrase strand transfer inhibitors (INSTIs)	Raltegravir	↔	↔	↑	↓
	Dolutegravir	↔	↔	↑	↓
	Bictegravir	↑	↓	↑	↓
	Cabotegravir	↓	↔	↑	↓

↑ = some increase. ↑ ↑ = moderate increase. ↓ = some decrease. ↔ = No significant change. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

3. Treatment of Dyslipidemia

The treatment of dyslipidemia in PLHIV reflects the eminent need to address its most common clinical consequence, atherosclerotic cardiovascular disease (ASCVD). ASCVD risk stratification in PLHIV is usually performed by assessing risk scores from the general population, such as the Framingham Heart Study (FHS-CVD), the Pooled Cohort equations of the American College of Cardiology/American Heart Association (PCE) and the Systematic Coronary Risk Evaluation High-Risk Equation (SCORE), in an attempt to detect early those with a high or very high risk of ASCVD.[142] Although practical and essential, the aforementioned scores systematically underestimate the CVD risk of PLHIV, especially among low / moderate risk groups, leading to inadequate or delayed treatment initiation.[143] Furthermore, although the therapeutic approach to dyslipidemia in HIV individuals aligns with that of the general population, in PLHIV, potential interactions between lipid-lowering drugs and antiretroviral treatment should be taken into account. The initial step of lipid management involves endorsing lifestyle modifications, followed by the introduction of lipid lowering therapy, although in individuals with an increased risk of cardiovascular disease, switching from HAART to more lipid-friendly regimens has a pivotal role.

3.1. Statins

Statins are the most commonly prescribed lipid-lowering agents and are considered the first drug of choice in PLHIV to reduce the risk of ASCVD, with seven statins currently available on the market, divided into generations depending on their origin, their synthetic compounds, and their hydrophilic or lipophilic properties.[144] Statins possess pleiotropic properties in addition to LDL reduction, consisting of inflammation deterioration, immune activation, oxidative stress, and endothelial dysfunction; a game-changing ability given the presence of persistent inflammation in HIV infection.[145] Notably, the Johns Hopkins HIV clinical cohort that enrolled 1538 virally suppressed HIV individuals under statin treatment, demonstrated a reduced risk of all-cause mortality, after adjusting for CD4 count, HIV-1 RNA, hemoglobin, and cholesterol levels at the start of HAART, age, race, HIV risk group, prior use of ART, year of HAART start, NNRTI versus PI-based ART, prior AIDS-defining illness, and viral hepatitis coinfection.[146] The aforementioned data are strengthened by a recent meta-analysis of 36,253 HIV individuals undergoing statin treatment, where statin use was independently statistically correlated with a reduced mortality risk in PLWH.[147]

3.1.1. The Role of Statins in Inflammation

Numerous pathophysiological pathways are involved in the pleiotropic effect of statins. As statins competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), which is responsible for the end-stage production of mevalonate, a proposed pathophysiological pathway involves the diminished formation of important isoprenoid intermediates such as farnesyl-

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pyrophosphate (FPP) and geranyl-geranyl-pyrophosphate.[148] These molecules are responsible for prenylation, a process that affects numerous signal transduction molecules in vascular and myocardial signaling pathways, such as small guanine triphosphate (GTP) binding proteins, which regulate pro-atherogenic pathways, the expression of pro-inflammatory cytokines and directly activating PPAR-γ in platelets, inflammatory cells, vascular wall cells, and cardiomyocytes.[149,150] Furthermore, statins upregulate endothelial nitric oxide synthase,[79] inducing enhanced NO bioavailability and promote its vasodilatory, anti-inflammatory and anti-atherogenic effects. In fact, inhibition of Rho kinases geranyl-geranyl phosphorylation and activation of the PI3-Akt protein kinase pathway are both associated with increased expression of the *eNOS* gene in human endothelial cells, while polyadenylation of eNOS mRNA and down-regulation of caveolin-1 expression led to stabilized eNOS mRNA and prolonged activation of eNOS.[150,151] In vitro studies have also demonstrated the significant effect of statins on inflammatory cells *per se*, interfering with the interaction between vascular smooth muscle cells (VSMC) and monocytes, resulting in decreased synergistic production of pro-inflammatory cytokines, particularly IL-6.[152,153] Interestingly, lovastatin appears to down-regulate nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1) in a dose-dependent manner, with concomitant suppression of key chemokines, including those regulated upon activation normal T-cell expressed and secreted (RANTES) and the MCP-1, resulting in reduced production of IL-2, IL-4, and IFN-γ, and ultimately decreasing the inflammatory cell infiltration of arterial walls. Furthermore, statins reduce oxLDL and increase apoA-I levels, decreasing the expression of E-selectin, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule (VCAM), eventually reducing TNF-a, IL-6 and CRP levels.[154–156] Several studies have also evaluated the circulating biomarkers associated with advanced atherosclerosis in people with HIV, with numerous statins having inconsistent reduction patterns of different biomarkers.[157] In a study of 98 individuals with HIV virologically suppressed, atorvastatin 20 mg daily reduced oxLDL by 33%, sCD14, sCD163, CRP, and markers of T cell and monocyte activation,[158] while a study by Calza et al. showed a substantial reduction of CRP, IL-6 and TNF-a levels, after a 12-month follow-up with 10 mg of rosuvastatin per day.[158,159] The JUPITER trial also brought to light important data regarding individuals with non-elevated LDL (LDL< 130 mg/dL), but with moderate inflammation (CRP ≥ 2 mg/L), showcasing a relative reduction of 44% in the levels of LDL and CRP compared to placebo, while the SATURN-HIV study demonstrated favorable outcomes in CD4+ and CD8+ activation markers under a 48-week rosuvastatin treatment, with concomitant 13.2% reduction of sCD14, an event associated with 21% decreased risk of all-cause mortality in PLHIV.[160,161]

3.1.2. The Role of Statins in Lipid Management

Although statins exhibit major pleotropic anti-inflammatory properties, their most profound effect in reducing the risk of ASCVD lies within their hypolipidemic effect. It is reported that a decrease in LDL of 2 mg / dL is associated with an average reduction of 1% in the risk of clinical events in the general population, however, some differences have been detected in PLHIV, as a reduction of 3-16% of total cholesterol was observed in PLHIV, compared to non-HIV.[11,162] Furthermore, the efficacy of statin in HIV-induced dyslipidemia is well established, Calza et al. providing evidence regarding different statin options, enrolling 94 HIV individuals in PI-based treatment with hypercholesterolaemia (TC > 250 mg/dL) of at least 3 months duration. In more detail, participants were randomized to hypolipidemic treatment with rosuvastatin 10 mg daily, pravastatin 20 mg daily or atorvastatin 10 mg daily, with results demonstrating a significantly higher mean decrease in TC levels with rosuvastatin (25.2%), rather than with pravastatin (17.6%) or atorvastatin (19.8%), after one year of follow up.[163–166] Another randomized control trial assessing statin efficacy, the INTREPID study, compared pitavastatin to pravastatin, and demonstrated a significantly higher reduction in LDL levels in PLHIV under 4mg of pitavastatin versus 40mg pravastatin (31% and 21% respectively) at 12 weeks of therapy, with the benefit being sustained at week 52.[167] Most notably, reductions in TC, non-HDL, apoB, apoB/apoA-I ratio, and TC/HDL ratio were also significantly in favor of pitavastatin, while no differences in apoA-I, TG or HDL were demonstrated at either week 12 or week 52. Furthermore, a recent meta-analysis demonstrated that 10 mg of rosuvastatin per day and 10 mg of atorvastatin per day provided the largest reduction in TC levels, while atorvastatin 80 mg and simvastatin 20 mg provided the greatest reduction in LDL levels,

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atorvastatin 80 mg and simvastatin 20 mg showed the greatest reduction in TG levels, while pravastatin 10-20 mg and atorvastatin 10 mg showed the largest increase in HDL levels.[11] The hallmark of statin treatment in prevention of ASCVD risk in PLHIV, and perhaps one of the most anticipated trials in the field of dyslipidemia, was the REPRIEVE trial. REPRIEVE was a large, randomized, blinded study of pitavastatin versus placebo in more than 7500 HIV individuals, and it demonstrated for the first time, a reduction in clinical endpoints (MACE), defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause. The study showed an incidence of 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group in MACE, but also used a pooled cohort equation for ASCVD risk stratification, thus providing an opportunity to evaluate statin benefits in those with higher and lower ASCVD risk.[168]

3.1.3. Drug Interactions between HAART and Statins

One of the main concerns with the use of statins in PLHIV is the potential drug-drug interactions with HAART agents, resulting in increased statin exposure and potential side effects, or decreased exposure and therapeutic failure, but also in alterations in antiretroviral bioavailability. Many HAART agents, especially PIs, pharmacokinetic boosters and NNRTIs, share common metabolic and deactivation pathways with statins, with both drug categories serving as substrates or inhibitors of cytochrome P450, particularly CYP3A4 and CYP2C9, and organic anion-transporting polypeptides (OATPs), while complex biliary excretion and active tubular secretion through CYP3A4, OATP1B1, P-glycoprotein (P-gp) and r breast cancer resistance protein (BCRP), enhance the intricacy of statin choice.

Rosuvastatin and fluvastatin are metabolized primarily by CYP2C9, while pravastatin is minimally metabolized by P450 enzymes, therefore they are considered safe options when combined with PIs and NNRTI, although rosuvastatin and pravastatin may demonstrate minor interactions due to inhibition of OATP1B1.[169] In fact, co-administration of rosuvastatin with ATV/r, has been associated with a significant increase in ATV concentration above the therapeutic threshold, with a concomitant risk of adverse drug reactions, while other studies demonstrated increased maximum concentration of rosuvastatin when co-administered with ATV, LPV or DRV/r of 600%, 366% and 139% respectively.[170,171] Therefore, if rosuvastatin is concomitantly administered with PIs, a low dose of 5 mg per day is recommended, with slow titration and close monitoring. Along the same line, studies regarding pravastatin have demonstrated an exposure decrease of 50% in patients receiving SQV/r and 40% in those receiving EFV, as well as an increase in AUC of 33% and 81% in PLHIV under LPV/r and DRV/r, respectively, thus guidelines recommend a suitable dose adjustment to achieve the expected benefit, especially with DRV/r.[172] Furthermore, clinically relevant interactions between fluvastatin and HAART have not been extensively documented, although co-administration with NFV and EFV could result in low plasma statin concentrations, hence a higher initial dose is suggested.[173] Lovastatin and simvastatin have extensive metabolism first pass by CYP3A4 and are contraindicated in HIV individuals under HHART, mainly due to the severe and fatal adverse effects upon concomitant use with PI-based regimens, alongside the easy access to safer statin options.[174,175]

Atorvastatin follows the same metabolic pathway, although to a lesser extent serves as a substrate for OATP1B1 and shows affinity for CYP3A4 and P-gp, therefore its concentration can differ with co-administration of PIs or NNRTIs. In fact, different studies presented contradictory evidence, due to the different pharmacokinetic interactions of atorvastatin and certain HAART agents.[176] In more detail, evidence has demonstrated an increased exposure of 79% in HIV individuals receiving SQV/r and nearly 488% with LPV/r, and thus guidelines recommend a submaximal initial dose of atorvastatin, 10 mg in ATV/r-containing regimens, 20 mg in LPV/r-containing regimens, and 40 mg DRV/r-containing regimens.[169,174] However, the potential reduction of atorvastatin AUC by 32% and 43% with ETV and EFV, respectively, highlights the necessity for increased dosage of atorvastatin, with a threshold of 80 mg per day.[177] Significant interactions due to inhibition of CYP3A4, P-gp and BCRP could present with concomitant use of cobicistat to enhance ATV, DRV and ELV, and despite data scarcity, the tendency is to initiate the lowest recommended dose, titrate carefully, and monitor for adverse effects, especially with atorvastatin and rosuvastatin.[178] Pitavastatin is mainly

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metabolized via glucuronidation and minimally by CYP450 enzymes and thus the potential for drug interactions through the CYP450 system are reduced, rendering pitavastatin a rather safe option with no interactions expected. Similarly, INSTIs do not pose a risk for drug-drug interaction, as they exhibit weak to no inhibition of BCRP and other metabolizing enzymes.

3.2. Ezetimibe

Ezetimibe inhibits the Niemann-Pick C1-like cholesterol transport protein (NPC1L1) at the brush border of the small intestine, leading to upregulation of LDL receptors and its circulatory clearance.[179] As ezetimibe does not interact with CYP3A4 and therefore is not associated with drug-drug interactions with HAART, it should be considered as a treatment option in PLHIV with statin intolerance, or as an additional therapy in those who already receive the maximum indicated statin dose and do not reach LDL therapeutic targets. Furthermore, the results of a recent meta-analysis of 13 randomized controlled trials and single-arm trials comparing rosuvastatin plus ezetimibe versus rosuvastatin monotherapy showed significant reductions in LDL levels (-23.89 mg/dl), TC (-26.17 mg/dl) and TG levels (-18.57 mg/dl), but no reduction in HDL levels with ezetimibe,[180] while other studies showed a mean decrease of -18.18 mg / dl versus -9mg / dl in TC levels, a mean decrease of -11.16 mg / dl versus -3 mg/dl in TG levels, and a mean decrease of -17.46 mg / dl versus -9.5 mg/dl in non-HDL levels.[181] Notably, numerous studies also demonstrated favorable outcomes with ezetimibe initiation with regard to inflammation markers, in particularly CRP, IL-1b and IL-18, providing In fact, reduction in adipocyte size, accumulation of pro-inflammatory cytokines, expression of TNF-a, and suppression of NF-kB activation have been associated with its use, making ezetimibe a rather strategic asset in the management of dyslipidemia in PLHIV.[182–185]

3.3. PCSK9 Inhibitors

It should be mentioned that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a heterogeneous group of molecules consisting of 2 monoclonal antibodies, alirocumab and evolocumab, and a synthetic small interfering RNA (siRNA), inclisiran, have currently emerged as treatment options for hyperlipidemia, and have been associated with a reduction in serum LDL levels through up-regulation of LDL receptors and increased LDL clearance.[186] PCSK9i is used as a third step approach in HIV individuals with increased risk of ASCVD who face intolerance or severe drug-drug interactions with statins, and also fall behind recommended LDL levels with statin plus ezetimibe interventions, offering an additional 43% to 64% reduction of LDL, alongside statins.[187] Although recent EACS guidelines included both evolocumab and alirocumab with their safety and efficacy already having been extensively documented in the FOURIER and ODYSSEY studies for the general population with no drug interactions having been reported, data are only available for evolocumab in PLHIV.[188,189] Among the first reports, a small single-center study with 19 HIV individuals, demonstrated favorable effects of evolocumab in LDL levels and coronary endothelial function, as measured by cine 3T MRI, setting the boundaries for the BEIJERINCK study.[190] In this study Boccara et al. enrolled 467 PLHIV with well-treated HIV infection and mean LDL levels at baseline 133 ± 40 mg/dl. In more detail, among the participants, 31% of them were under statins, 21% had a history of statin intolerance and 40% had potential drug-drug interactions between statins and HAART. The results showed a persistent reduction in LDL levels of 58% through 52 weeks of exposure, with a concomitant sustained improvement in TC, TG, non-HDL, VLDL, apoB, Lp(a) and HDL levels, which highlights the beneficial role of PCSK9 in PLHIV with advanced hyperlipidemia.[191] Although the underlying mechanisms are still poorly understood, experimental models and clinical trials of individuals from the general population with familial hypercholesterolemia have shown reduced expression of ICAM-1 and CCR2 in monocytes, as well as down-regulation of TNF-a, IL-1 and IL-6, and up-regulation of IL-10 with PCSK9i, highlighting the potential anti-inflammatory properties of PCSK9i in PLHIV.[192,193]

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3.3. Bemdedoic Acid

Bempedoic acid, a recently approved hypolipidemic agent for adults with heterozygous familial hypercholesterolemia or established risk of ASCVD, has shown impressive LDL lowering properties, as monotherapy or in combination with ezetimibe, through inhibition of ATP citrate lyase (ACLY) alongside direct activation of AMP-activated protein kinase (AMPK).[194,195] Although some studies have shown favorable results for statin intolerant patients or those under maximally tolerated statin dose of the general population, data from HIV individuals are scarce at the present. The randomized CLEAR trial showed a reduction in LDL levels of 17.8% and 24.5% among statin-treated and statin-intolerant patients, respectively, with a concomitant reduction of 18.1% in CRP levels, while recently published data from the same trial with 13,970 statin-intolerant participants, reported a reduction in all major adverse cardiovascular events with the use of bempedoic acid.[196,197] Furthermore, Ballantyne et al. enrolled 301 patients with increased risk of ASCVD undergoing statin therapy in a phase 3, double-blind clinical trial, and randomly assigned them to a fixed dose of bempedoic acid plus ezetimibe, bempedoic acid as monotherapy, ezetimibe alone or placebo, showcasing a 36.2% reduction of LDL levels with combination treatment, 23.2% reduction with ezetimibe and 17.2% reduction with bempedoic acid as monotherapy.[198] The aforementioned evidence, alongside the lack of drug interactions or considerable muscle-related side effects, have led the updated EACS guidelines to enlist 180mg of bempedoic acid once daily, as a potential therapeutic approach in HIV individuals with unmet LDL goals.[198]

3.4. Fibrates

A significant metabolic disorder and a predominant abnormal lipid characteristic in HIV infection are considered hypertriglyceridemia. The cornerstone of its treatment remains to this day lifestyle modifications, aiming at TG levels < 150 mg/dL, followed by statin treatment for HIV individuals with increased risk of ASCVD and TG> 200 mg / dl; however, treatment for markedly elevated TG levels > 500 mg/dL or even above this range, usually requires fibrate initiation, due to the increased risk of pancreatitis.[200] Fibrates act by binding and activating the nuclear hormone receptor peroxisome proliferator activated receptor (PPAR-α), inducing PPAR-dependent gene transcription and upregulating lipoprotein lipase, thus limiting substrate availability in the liver for TG synthesis and increasing TG clearance.[201] On the same side, activation of PPAR-a leads to decreased production of pro-inflammatory mediators such as TNF-a, IL-1, IL-6 and IL-8, while also promoting the production of anti-inflammatory agents, such as IL-10, thus contributing to inflammatory retention in HIV infection.[202] Fenofibrate lacks significant interactions with ART, while gemfibrozil's inhibition of OATP might result in increased systemic exposure when co-administered with specific HAART regimens such as LPV/r, but it can also lead to decreased hypolipidemic efficacy and increased serum concentrations of statins.[203,204] Furthermore, a study by Silverberg et al. with 6941 HIV individuals, demonstrated a substantially lower reduction of TG levels in PLHIV as compared with the general population, with great variation among individual HAART classes, -44.0% in patients receiving PI monotherapy, -26.4% in patients receiving PIs and NNRTIs, and -60.3% in patients receiving NNRTIs.[205] Amongst fibrates, gemfibrozil seems to be more effective in PWH as compared with fenofibrate, with a mean TG reduction of 80 mg/dL and 49 mg/dL respectively, while in combination with ezetimibe it achieved remarkable reduction in TG levels (from 265 ± 118 mg/dl to 149 ± 37 mg/dl,) and a considerable augmentation of HDL levels (44 ± 10 to 53 ± 12 mg/dl), in comparison with statins.[206,207] Although their hypolipidemic effect is solid, fibrates failed to reduce the incidence of cardiovascular events of more than 10,000 patients with increased ASCVD risk in the PROMINENT study that was conducted with participants from the general population, therefore, similar long-scale studies in HIV population seem to be imperative.[208]

3.5. Fish Oils

Fish oils are long-chain omega-3 polyunsaturated fatty acids (PUFAs), and their two purified forms of ethyl esterized n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are commonly used to decrease TG levels and the risk of ASCVD in the general population. Their hypolipidemic effect, along with their anti-inflammatory properties that have been attributed to inhibition of VLDL production, has been well documented in the REDUCE-IT trial. This study, in

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which 8,179 statin-treated patients with elevated TG levels and cardiovascular disease or diabetes were randomized to 4g of icosapent ethyl per day or placebo, showed a 25% relative and 4.8% absolute reduction in the primary end points of MACE, except death from any cause, while the REDUCE-IT biomarker substudy demonstrated a significant reduction in serum levels of IL-1, IL-6, CRP, oxLDL, homocysteine, Lp(a) and lipoprotein-associated phospholipase A2, thus establishing EPA as a promising therapeutic option to combat hypertriglyceridemia.[209,210] Although limited, evidence for PLHIV has validated the beneficial effect of PUFAs, especially for EPA. A double-blind, placebo-controlled study that randomized 48 PLHIV under fibrate or niacin with 4 gr PUFA daily versus placebo for 12 weeks showed a reduction of 31.5 mg/dL and 7.4 mg/dl in TG levels, respectively, while the ACTG A5186 study randomized 100 PLHIV with TG levels >400 mg/dL to 3 gr of fish oil twice daily or 160 mg of fenofibrate daily for 8 weeks, demonstrated a 46% and 58% reduction in TG levels in each arm, respectively, with combination treatment of both fish oil and fenofibrate resulting in a total 65.5% reduction, achieving TG levels < 200 mg/dL in 22.7% of the patients.[211,212] Along the same line, similar evidence was also reported from a recent meta-analysis of clinical trials assessing the efficacy of PUFAs and especially EPA in PLHIV, with a 10.5 mg/dL reduction in TG levels and 11 mg/dL increase in HDL levels.[213] Therefore, fish oils seem to be a valuable asset against hypertriglyceridemia without major adverse effects or interactions, however, pill burden in a population under polypharmacy might interfere with patient compliance.

4. Conclusions

To the present day, dyslipidemia in PLHIV remains a challenge given the high prevalence of age-related metabolic diseases and the multifactorial origin of these comorbidities in inflammation and immune activation, with HIV viremia and antiretroviral treatment representing two sides of the same coin. Current antiretroviral regimens stand as safe, effective, and well-tolerated options in terms of HIV suppression; however, different HAART classes and drugs within the same class are held responsible for inducing lipid abnormalities, while considerable drug-drug interactions with major hypolipidemic agents raise concerns when treating dyslipidemia. The aim of careful evaluation of potential resistance, tolerability, adherence, modification, or substitution of HAART seems to be a game-changing strategy. Switching from RTV-based or RTV boosted regimens to DRV or AZT-based ones if PIs are required, avoiding thymidine analogs and favoring ABC and TDF in terms of NNRTI utilization, combined with shifting from EFV to NVP or RPV and incorporating lipid-friendly INSTIs, could maintain optimal viral response without the burden of associated dyslipidemia. In general, pharmacological interventions in PLHIV follow the guidelines for the HIV-negative population and are based on statin implementations; however, drug interactions mainly due to CYP450 metabolism of both statins and HAART could interfere with favorable outcomes. Add-on therapy with ezetimibe, PCSK9, bempedoic acid, fibrates or fish oils is recommended for individuals presenting with intolerance or unmet therapeutic targets, although large-scale clinical data are still scarce. An in-depth understanding of the underlying molecular mechanisms involved in HIV-associated dyslipidemia is imperative to achieve effective and personalized treatment with respect to HAART switching and hyperlipidemia, while future large-scale studies in HIV individuals that implement new lipid-lowering drugs are expected to optimize the management of metabolic-related comorbidities in PLHIV.

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References

1. World Health, O. *Global health sector strategy on HIV 2016-2021. Towards ending AIDS*; World Health Organization: Geneva, 2016 2016.

2. Thaker, H.K.; Snow, M.H. HIV viral suppression in the era of antiretroviral therapy. *Postgrad Med J* **2003**, *79*, 36-42, doi:10.1136/pmj.79.927.36.
3. Kaufmann, G.R.; Zaunders, J.; Cooper, D.A. Immune reconstitution in HIV-1 infected subjects treated with potent antiretroviral therapy. *Sex Transm Infect* **1999**, *75*, 218-224, doi:10.1136/sti.75.4.218.
4. Porter, K.; Babiker, A.; Bhaskaran, K.; Darbyshire, J.; Pezzotti, P.; Porter, K.; Walker, A.S.; Collaboration, C. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet* **2003**, *362*, 1267-1274, doi:10.1016/s0140-6736(03)14570-9.
5. Enanoria, W.T.; Ng, C.; Saha, S.R.; Colford, J.M., Jr. Treatment outcomes after highly active antiretroviral therapy: a meta-analysis of randomised controlled trials. *Lancet Infect Dis* **2004**, *4*, 414-425, doi:10.1016/S1473-3099(04)01057-6.
6. Smit, M.; Brinkman, K.; Geerlings, S.; Smit, C.; Thyagarajan, K.; Sighem, A.; de Wolf, F.; Hallett, T.B.; cohort, A.o. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis* **2015**, *15*, 810-818, doi:10.1016/S1473-3099(15)00056-0.
7. Expert Panel on Detection, E.; Treatment of High Blood Cholesterol in, A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* **2001**, *285*, 2486-2497, doi:10.1001/jama.285.19.2486.
8. Koethe, J.R. Adipose Tissue in HIV Infection. *Compr Physiol* **2017**, *7*, 1339-1357, doi:10.1002/cphy.c160028.
9. Masenga, S.K.; Elijovich, F.; Koethe, J.R.; Hamooya, B.M.; Heimburger, D.C.; Munsaka, S.M.; Laffer, C.L.; Kirabo, A. Hypertension and Metabolic Syndrome in Persons with HIV. *Curr Hypertens Rep* **2020**, *22*, 78, doi:10.1007/s11906-020-01089-3.
10. Freiberg, M.S.; Chang, C.H.; Skanderson, M.; Patterson, O.V.; DuVall, S.L.; Brandt, C.A.; So-Armah, K.A.; Vasan, R.S.; Oursler, K.A.; Gottdiener, J.; et al. Association Between HIV Infection and the Risk of Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction in the Antiretroviral Therapy Era: Results From the Veterans Aging Cohort Study. *JAMA Cardiol* **2017**, *2*, 536-546, doi:10.1001/jamacardio.2017.0264.
11. Gili, S.; Grosso Marra, W.; D'Ascenzo, F.; Lonni, E.; Calcagno, A.; Cannillo, M.; Ballocca, F.; Cerrato, E.; Pianelli, M.; Barbero, U.; et al. Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis. *Eur Heart J* **2016**, *37*, 3600-3609, doi:10.1093/eurheartj/ehv734.
12. Freiberg, M.S.; Chang, C.C.; Kuller, L.H.; Skanderson, M.; Lowy, E.; Kraemer, K.L.; Butt, A.A.; Bidwell Goetz, M.; Leaf, D.; Oursler, K.A.; et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* **2013**, *173*, 614-622, doi:10.1001/jamainternmed.2013.3728.
13. Tseng, Z.H.; Secemsky, E.A.; Dowdy, D.; Vittinghoff, E.; Moyers, B.; Wong, J.K.; Havlir, D.V.; Hsue, P.Y. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol* **2012**, *59*, 1891-1896, doi:10.1016/j.jacc.2012.02.024.
14. Ryom, L.; Lundgren, J.D.; El-Sadr, W.; Reiss, P.; Kirk, O.; Law, M.; Phillips, A.; Weber, R.; Fontas, E.; d' Arminio Monforte, A.; et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV* **2018**, *5*, e291-e300, doi:10.1016/S2352-3018(18)30043-2.
15. Hsue, P.Y.; Waters, D.D. Time to Recognize HIV Infection as a Major Cardiovascular Risk Factor. *Circulation* **2018**, *138*, 1113-1115, doi:10.1161/CIRCULATIONAHA.118.036211.
16. Feingold, K.R.; Krauss, R.M.; Pang, M.; Doerrler, W.; Jensen, P.; Grunfeld, C. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab* **1993**, *76*, 1423-1427, doi:10.1210/jcem.76.6.8501146.
17. Buchacz, K.; Baker, R.K.; Palella, F.J., Jr.; Shaw, L.; Patel, P.; Lichtenstein, K.A.; Chmiel, J.S.; Vellozzi, C.; Debes, R.; Henry, K.; et al. Disparities in prevalence of key chronic diseases by gender and race/ethnicity among antiretroviral-treated HIV-infected adults in the US. *Antivir Ther* **2013**, *18*, 65-75, doi:10.3851/IMP2450.
18. Riddler, S.A.; Smit, E.; Cole, S.R.; Li, R.; Chmiel, J.S.; Dobs, A.; Palella, F.; Visscher, B.; Evans, R.; Kingsley, L.A. Impact of HIV infection and HAART on serum lipids in men. *JAMA* **2003**, *289*, 2978-2982, doi:10.1001/jama.289.22.2978.
19. Sviridov, D.; Mukhamedova, N.; Makarov, A.A.; Adzhubei, A.; Bukrinsky, M. Comorbidities of HIV infection: role of Nef-induced impairment of cholesterol metabolism and lipid raft functionality. *AIDS* **2020**, *34*, 1-13, doi:10.1097/QAD.0000000000002385.
20. Mohseni Ahooyi, T.; Shekarabi, M.; Torkzaban, B.; Langford, T.D.; Burdo, T.H.; Gordon, J.; Datta, P.K.; Amini, S.; Khalili, K. Dysregulation of Neuronal Cholesterol Homeostasis upon Exposure to HIV-1 Tat and Cocaine Revealed by RNA-Sequencing. *Sci Rep* **2018**, *8*, 16300, doi:10.1038/s41598-018-34539-9.
21. Reeds, D.N.; Mittendorfer, B.; Patterson, B.W.; Powderly, W.G.; Yarasheski, K.E.; Klein, S. Alterations in lipid kinetics in men with HIV-dyslipidemia. *Am J Physiol Endocrinol Metab* **2003**, *285*, E490-497, doi:10.1152/ajpendo.00118.2003.

22. Duong, M.; Petit, J.M.; Martha, B.; Galland, F.; Piroth, L.; Walldner, A.; Grappin, M.; Buisson, M.; Duvillard, L.; Chavanet, P.; et al. Concentration of circulating oxidized LDL in HIV-infected patients treated with antiretroviral agents: relation to HIV-related lipodystrophy. *HIV Clin Trials* **2006**, *7*, 41-47, doi:10.1310/7381-m1yd-rtv5-4ryt.
23. Mujawar, Z.; Rose, H.; Morrow, M.P.; Pushkarsky, T.; Dubrovsky, L.; Mukhamedova, N.; Fu, Y.; Dart, A.; Orenstein, J.M.; Bobryshev, Y.V.; et al. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol* **2006**, *4*, e365, doi:10.1371/journal.pbio.0040365.
24. Damouche, A.; Lazure, T.; Avettand-Fenoel, V.; Huot, N.; Dejucq-Rainsford, N.; Satie, A.P.; Melard, A.; David, L.; Gommet, C.; Ghosn, J.; et al. Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection. *PLoS Pathog* **2015**, *11*, e1005153, doi:10.1371/journal.ppat.1005153.
25. Gorwood, J.; Bourgeois, C.; Mantecon, M.; Atlan, M.; Pourcher, V.; Pourcher, G.; Le Grand, R.; Desjardins, D.; Feve, B.; Lambotte, O.; et al. Impact of HIV/simian immunodeficiency virus infection and viral proteins on adipose tissue fibrosis and adipogenesis. *AIDS* **2019**, *33*, 953-964, doi:10.1097/QAD.0000000000002168.
26. Maurin, T.; Saillan-Barreau, C.; Cousin, B.; Casteilla, L.; Doglio, A.; Penicaud, L. Tumor necrosis factor-alpha stimulates HIV-1 production in primary culture of human adipocytes. *Exp Cell Res* **2005**, *304*, 544-551, doi:10.1016/j.yexcr.2004.12.003.
27. Munier, S.; Borjabad, A.; Lemaire, M.; Mariot, V.; Hazan, U. In vitro infection of human primary adipose cells with HIV-1: a reassessment. *AIDS* **2003**, *17*, 2537-2539, doi:10.1097/00002030-200311210-00019.
28. Tall, A.R.; Yvan-Charvet, L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol* **2015**, *15*, 104-116, doi:10.1038/nri3793.
29. Lake, J.E.; Currier, J.S. Metabolic disease in HIV infection. *Lancet Infect Dis* **2013**, *13*, 964-975, doi:10.1016/S1473-3099(13)70271-8.
30. Anastos, K.; Lu, D.; Shi, Q.; Tien, P.C.; Kaplan, R.C.; Hessol, N.A.; Cole, S.; Vigen, C.; Cohen, M.; Young, M.; et al. Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens. *J Acquir Immune Defic Syndr* **2007**, *45*, 34-42, doi:10.1097/QAI.0b013e318042d5fe.
31. Zhao, R.Y.; Bukrinsky, M.I. HIV-1 accessory proteins: VpR. *Methods Mol Biol* **2014**, *1087*, 125-134, doi:10.1007/978-1-62703-670-2_11.
32. Evans, R.M.; Barish, G.D.; Wang, Y.X. PPARs and the complex journey to obesity. *Nat Med* **2004**, *10*, 355-361, doi:10.1038/nm1025.
33. Francis, G.A.; Li, G.; Casey, R.; Wang, J.; Cao, H.; Leff, T.; Hegele, R.A. Peroxisomal proliferator activated receptor-gamma deficiency in a Canadian kindred with familial partial lipodystrophy type 3 (FPLD3). *BMC Med Genet* **2006**, *7*, 3, doi:10.1186/1471-2350-7-3.
34. Agarwal, N.; Iyer, D.; Gabbi, C.; Saha, P.; Patel, S.G.; Mo, Q.; Chang, B.; Goswami, B.; Schubert, U.; Kopp, J.B.; et al. HIV-1 viral protein R (Vpr) induces fatty liver in mice via LXRalpha and PPARalpha dysregulation: implications for HIV-specific pathogenesis of NAFLD. *Sci Rep* **2017**, *7*, 13362, doi:10.1038/s41598-017-13835-w.
35. Shrivastav, S.; Kino, T.; Cunningham, T.; Ichijo, T.; Schubert, U.; Heinklein, P.; Chrousos, G.P.; Kopp, J.B. Human immunodeficiency virus (HIV)-1 viral protein R suppresses transcriptional activity of peroxisome proliferator-activated receptor gamma and inhibits adipocyte differentiation: implications for HIV-associated lipodystrophy. *Mol Endocrinol* **2008**, *22*, 234-247, doi:10.1210/me.2007-0124.
36. Rice, A.P. The HIV-1 Tat Protein: Mechanism of Action and Target for HIV-1 Cure Strategies. *Curr Pharm Des* **2017**, *23*, 4098-4102, doi:10.2174/1381612823666170704130635.
37. Liu, Y.; Jones, M.; Hingtgen, C.M.; Bu, G.; Laribee, N.; Tanzi, R.E.; Moir, R.D.; Nath, A.; He, J.J. Uptake of HIV-1 tat protein mediated by low-density lipoprotein receptor-related protein disrupts the neuronal metabolic balance of the receptor ligands. *Nat Med* **2000**, *6*, 1380-1387, doi:10.1038/82199.
38. Weiss, J.M.; Nath, A.; Major, E.O.; Berman, J.W. HIV-1 Tat induces monocyte chemoattractant protein-1-mediated monocyte transmigration across a model of the human blood-brain barrier and up-regulates CCR5 expression on human monocytes. *J Immunol* **1999**, *163*, 2953-2959.
39. Zauli, G.; Furlini, G.; Re, M.C.; Milani, D.; Capitani, S.; La Placa, M. Human immunodeficiency virus type 1 (HIV-1) tat-protein stimulates the production of interleukin-6 (IL-6) by peripheral blood monocytes. *New Microbiol* **1993**, *16*, 115-120.
40. van 't Wout, A.B.; Swain, J.V.; Schindler, M.; Rao, U.; Pathmajeyan, M.S.; Mullins, J.I.; Kirchhoff, F. Nef induces multiple genes involved in cholesterol synthesis and uptake in human immunodeficiency virus type 1-infected T cells. *J Virol* **2005**, *79*, 10053-10058, doi:10.1128/JVI.79.15.10053-10058.2005.
41. Lin, S.; Nadeau, P.E.; Wang, X.; Mergia, A. Caveolin-1 reduces HIV-1 infectivity by restoration of HIV Nef mediated impairment of cholesterol efflux by apoA-I. *Retrovirology* **2012**, *9*, 85, doi:10.1186/1742-4690-9-85.
42. Lin, S.; Nadeau, P.E.; Mergia, A. HIV inhibits endothelial reverse cholesterol transport through impacting subcellular Caveolin-1 trafficking. *Retrovirology* **2015**, *12*, 62, doi:10.1186/s12977-015-0188-y.

43. Duffy, P.; Wang, X.; Lin, P.H.; Yao, Q.; Chen, C. HIV Nef protein causes endothelial dysfunction in porcine pulmonary arteries and human pulmonary artery endothelial cells. *J Surg Res* **2009**, *156*, 257-264, doi:10.1016/j.jss.2009.02.005.
44. Olivetta, E.; Percario, Z.; Fiorucci, G.; Mattia, G.; Schiavoni, I.; Dennis, C.; Jager, J.; Harris, M.; Romeo, G.; Affabris, E.; et al. HIV-1 Nef induces the release of inflammatory factors from human monocyte/macrophages: involvement of Nef endocytotic signals and NF-kappa B activation. *J Immunol* **2003**, *170*, 1716-1727, doi:10.4049/jimmunol.170.4.1716.
45. Wang, T.; Green, L.A.; Gupta, S.K.; Kim, C.; Wang, L.; Almodovar, S.; Flores, S.C.; Prudovsky, I.A.; Jolicoeur, P.; Liu, Z.; et al. Transfer of intracellular HIV Nef to endothelium causes endothelial dysfunction. *PLoS One* **2014**, *9*, e91063, doi:10.1371/journal.pone.0091063.
46. Schipper, H.S.; Prakken, B.; Kalkhoven, E.; Boes, M. Adipose tissue-resident immune cells: key players in immunometabolism. *Trends Endocrinol Metab* **2012**, *23*, 407-415, doi:10.1016/j.tem.2012.05.011.
47. Dorfmuller, P.; Zarka, V.; Durand-Gasselin, I.; Monti, G.; Balabanian, K.; Garcia, G.; Capron, F.; Coulomb-Lhermine, A.; Marfaing-Koka, A.; Simonneau, G.; et al. Chemokine RANTES in severe pulmonary arterial hypertension. *Am J Respir Crit Care Med* **2002**, *165*, 534-539, doi:10.1164/ajrccm.165.4.2012112.
48. Freeman, M.L.; Hossain, M.B.; Burrowes, S.A.B.; Jeudy, J.; Bui, R.; Moisi, D.; Mitchell, S.E.; Khambaty, M.; Weiss, R.G.; Lederman, M.M.; et al. Association of Soluble Markers of Inflammation With Peri-coronary Artery Inflammation in People With and Without HIV Infection and Without Cardiovascular Disease. *Open Forum Infect Dis* **2023**, *10*, ofad328, doi:10.1093/ofid/ofad328.
49. Couturier, J.; Agarwal, N.; Nehete, P.N.; Baze, W.B.; Barry, M.A.; Jagannadha Sastry, K.; Balasubramanyam, A.; Lewis, D.E. Infectious SIV resides in adipose tissue and induces metabolic defects in chronically infected rhesus macaques. *Retrovirology* **2016**, *13*, 30, doi:10.1186/s12977-016-0260-2.
50. McGillicuddy, F.C.; de la Llera Moya, M.; Hinkle, C.C.; Joshi, M.R.; Chiquoine, E.H.; Billheimer, J.T.; Rothblat, G.H.; Reilly, M.P. Inflammation impairs reverse cholesterol transport in vivo. *Circulation* **2009**, *119*, 1135-1145, doi:10.1161/CIRCULATIONAHA.108.810721.
51. Khovidhunkit, W.; Memon, R.A.; Feingold, K.R.; Grunfeld, C. Infection and inflammation-induced proatherogenic changes of lipoproteins. *J Infect Dis* **2000**, *181 Suppl 3*, S462-472, doi:10.1086/315611.
52. Perrotta, I.; Aquila, S. The role of oxidative stress and autophagy in atherosclerosis. *Oxid Med Cell Longev* **2015**, *2015*, 130315, doi:10.1155/2015/130315.
53. Ma, R.; Yang, L.; Niu, F.; Buch, S. HIV Tat-Mediated Induction of Human Brain Microvascular Endothelial Cell Apoptosis Involves Endoplasmic Reticulum Stress and Mitochondrial Dysfunction. *Mol Neurobiol* **2016**, *53*, 132-142, doi:10.1007/s12035-014-8991-3.
54. Cross, A.R.; Segal, A.W. The NADPH oxidase of professional phagocytes--prototype of the NOX electron transport chain systems. *Biochim Biophys Acta* **2004**, *1657*, 1-22, doi:10.1016/j.bbabio.2004.03.008.
55. Strowig, T.; Henao-Mejia, J.; Elinav, E.; Flavell, R. Inflammasomes in health and disease. *Nature* **2012**, *481*, 278-286, doi:10.1038/nature10759.
56. Guo, H.; Gao, J.; Taxman, D.J.; Ting, J.P.; Su, L. HIV-1 infection induces interleukin-1beta production via TLR8 protein-dependent and NLRP3 inflammasome mechanisms in human monocytes. *J Biol Chem* **2014**, *289*, 21716-21726, doi:10.1074/jbc.M114.566620.
57. Blanc, M.; Hsieh, W.Y.; Robertson, K.A.; Watterson, S.; Shui, G.; Lacaze, P.; Khondoker, M.; Dickinson, P.; Sing, G.; Rodriguez-Martin, S.; et al. Host defense against viral infection involves interferon mediated down-regulation of sterol biosynthesis. *PLoS Biol* **2011**, *9*, e1000598, doi:10.1371/journal.pbio.1000598.
58. Vyboh, K.; Jenabian, M.A.; Mehraj, V.; Routy, J.P. HIV and the gut microbiota, partners in crime: breaking the vicious cycle to unearth new therapeutic targets. *J Immunol Res* **2015**, *2015*, 614127, doi:10.1155/2015/614127.
59. Serrano-Villar, S.; Vazquez-Castellanos, J.F.; Vallejo, A.; Latorre, A.; Sainz, T.; Ferrando-Martinez, S.; Rojo, D.; Martinez-Botas, J.; Del Romero, J.; Madrid, N.; et al. The effects of prebiotics on microbial dysbiosis, butyrate production and immunity in HIV-infected subjects. *Mucosal Immunol* **2017**, *10*, 1279-1293, doi:10.1038/mi.2016.122.
60. Nordell, A.D.; McKenna, M.; Borges, A.H.; Duprez, D.; Neuhaus, J.; Neaton, J.D.; Insight Smart, E.S.G.; Committee, S.S. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. *J Am Heart Assoc* **2014**, *3*, e000844, doi:10.1161/JAHA.114.000844.
61. Villanueva-Millan, M.J.; Perez-Matute, P.; Recio-Fernandez, E.; Lezana Rosales, J.M.; Oteo, J.A. Characterization of gut microbiota composition in HIV-infected patients with metabolic syndrome. *J Physiol Biochem* **2019**, *75*, 299-309, doi:10.1007/s13105-019-00673-9.
62. Ambrosioni, J.; Levi, L.; Alagaratnam, J.; Van Bremen, K.; Mastrangelo, A.; Waalewijn, H.; Molina, J.M.; Guaraldi, G.; Winston, A.; Boesecke, C.; et al. Major revision version 12.0 of the European AIDS Clinical Society guidelines 2023. *HIV Med* **2023**, *24*, 1126-1136, doi:10.1111/hiv.13542.
63. Okunorobo, M.N.; Nnamah, N.K.; Ude, U.A.; Ude, E.A. Lipids and apolipoproteins C-III and E among treatment-naive and treatment-experienced persons with HIV in Nigeria. *Afr J Lab Med* **2023**, *12*, 2018, doi:10.4102/ajlm.v12i1.2018.

64. Lu, L.; Yang, Y.; Yang, Z.; Wu, Y.; Liu, X.; Li, X.; Chen, L.; Han, Y.; Song, X.; Kong, Z.; et al. Altered plasma metabolites and inflammatory networks in HIV-1 infected patients with different immunological responses after long-term antiretroviral therapy. *Front Immunol* **2023**, *14*, 1254155, doi:10.3389/fimmu.2023.1254155.
65. Mandal, A.; Mukherjee, A.; Lakshmy, R.; Kabra, S.K.; Lodha, R. Dyslipidemia in HIV Infected Children Receiving Highly Active Antiretroviral Therapy. *Indian J Pediatr* **2016**, *83*, 226-231, doi:10.1007/s12098-015-1859-3.
66. Ambisa Lamesa, T.; Getachew Mamo, A.; Arega Berihun, G.; Alemu Kebede, R.; Bekele Lemesa, E.; Cheneke Gebisa, W. Dyslipidemia and Nutritional Status of HIV-Infected Children and Adolescents on Antiretroviral Treatment at the Comprehensive Chronic Care and Training Center of Jimma Medical Center. *HIV AIDS (Auckl)* **2023**, *15*, 537-547, doi:10.2147/HIV.S418729.
67. Li, X.; Song, X.; Han, Y.; Qiu, Z.; Cao, W.; Li, T. Risk factors and longitudinal changes of dyslipidemia among Chinese people living with HIV receiving antiretroviral therapy. *BMC Infect Dis* **2023**, *23*, 598, doi:10.1186/s12879-023-08587-0.
68. Mallon, P.W.; Cooper, D.A.; Carr, A. HIV-associated lipodystrophy. *HIV Med* **2001**, *2*, 166-173, doi:10.1046/j.1468-1293.2001.00071.x.
69. Woo, S.R.; Turnis, M.E.; Goldberg, M.V.; Bankoti, J.; Selby, M.; Nirschl, C.J.; Bettini, M.L.; Gravano, D.M.; Vogel, P.; Liu, C.L.; et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* **2012**, *72*, 917-927, doi:10.1158/0008-5472.CAN-11-1620.
70. Feeney, E.R.; Mallon, P.W. HIV and HAART-Associated Dyslipidemia. *Open Cardiovasc Med J* **2011**, *5*, 49-63, doi:10.2174/1874192401105010049.
71. Martini, S.; Pisaturo, M.; Russo, A.; Palamone, M.G.; Russo, M.T.; Zollo, V.; Maggi, P.; Coppola, N. Evaluation of Lipid Profile and Intima Media Thickness in Antiretroviral-Experienced HIV-Infected Patients Treated with Protease Inhibitor-Based Regimens versus Protease Inhibitor-Sparing Regimens. *Pathogens* **2023**, *12*, doi:10.3390/pathogens12070925.
72. den Boer, M.A.; Berbee, J.F.; Reiss, P.; van der Valk, M.; Voshol, P.J.; Kuipers, F.; Havekes, L.M.; Rensen, P.C.; Romijn, J.A. Ritonavir impairs lipoprotein lipase-mediated lipolysis and decreases uptake of fatty acids in adipose tissue. *Arterioscler Thromb Vasc Biol* **2006**, *26*, 124-129, doi:10.1161/01.ATV.0000194073.87647.10.
73. Caron, M.; Auclair, M.; Sterlingot, H.; Kornprobst, M.; Capeau, J. Some HIV protease inhibitors alter lamin A/C maturation and stability, SREBP-1 nuclear localization and adipocyte differentiation. *AIDS* **2003**, *17*, 2437-2444, doi:10.1097/00002030-200311210-00005.
74. Caron, M.; Auclair, M.; Vigouroux, C.; Glorian, M.; Forest, C.; Capeau, J. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* **2001**, *50*, 1378-1388, doi:10.2337/diabetes.50.6.1378.
75. Zhou, H.; Gurley, E.C.; Jarujaron, S.; Ding, H.; Fang, Y.; Xu, Z.; Pandak, W.M., Jr.; Hylemon, P.B. HIV protease inhibitors activate the unfolded protein response and disrupt lipid metabolism in primary hepatocytes. *Am J Physiol Gastrointest Liver Physiol* **2006**, *291*, G1071-1080, doi:10.1152/ajpgi.00182.2006.
76. Liang, J.S.; Distler, O.; Cooper, D.A.; Jamil, H.; Deckelbaum, R.J.; Ginsberg, H.N.; Sturley, S.L. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: a potential mechanism for protease inhibitor-induced hyperlipidemia. *Nat Med* **2001**, *7*, 1327-1331, doi:10.1038/nm1201-1327.
77. Akita, S.; Suzuki, K.; Yoshimoto, H.; Ohtsuru, A.; Hirano, A.; Yamashita, S. Cellular Mechanism Underlying Highly-Active or Antiretroviral Therapy-Induced Lipodystrophy: Atazanavir, a Protease Inhibitor, Compromises Adipogenic Conversion of Adipose-Derived Stem/Progenitor Cells through Accelerating ER Stress-Mediated Cell Death in Differentiating Adipocytes. *Int J Mol Sci* **2021**, *22*, doi:10.3390/ijms22042114.
78. Friis-Moller, N.; Weber, R.; Reiss, P.; Thiebaut, R.; Kirk, O.; d'Arminio Monforte, A.; Pradier, C.; Morfeldt, L.; Mateu, S.; Law, M.; et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. *AIDS* **2003**, *17*, 1179-1193, doi:10.1097/01.aids.0000060358.78202.c1.
79. Fontas, E.; van Leth, F.; Sabin, C.A.; Friis-Moller, N.; Rickenbach, M.; d'Arminio Monforte, A.; Kirk, O.; Dupon, M.; Morfeldt, L.; Mateu, S.; et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis* **2004**, *189*, 1056-1074, doi:10.1086/381783.
80. Sadler, B.M.; Piliero, P.J.; Preston, S.L.; Lloyd, P.P.; Lou, Y.; Stein, D.S. Pharmacokinetics and safety of amprenavir and ritonavir following multiple-dose, co-administration to healthy volunteers. *AIDS* **2001**, *15*, 1009-1018, doi:10.1097/00002030-200105250-00009.
81. Purnell, J.Q.; Zambon, A.; Knopp, R.H.; Pizzuti, D.J.; Achari, R.; Leonard, J.M.; Locke, C.; Brunzell, J.D. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* **2000**, *14*, 51-57, doi:10.1097/00002030-200001070-00006.

82. Shafran, S.D.; Mashinter, L.D.; Roberts, S.E. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. *HIV Med* **2005**, *6*, 421-425, doi:10.1111/j.1468-1293.2005.00328.x.
83. Lee, G.A.; Seneviratne, T.; Noor, M.A.; Lo, J.C.; Schwarz, J.M.; Aweeka, F.T.; Mulligan, K.; Schambelan, M.; Grunfeld, C. The metabolic effects of lopinavir/ritonavir in HIV-negative men. *AIDS* **2004**, *18*, 641-649, doi:10.1097/00002030-200403050-00008.
84. Voigt, E.; Wasmuth, J.C.; Vogel, M.; Mauss, S.; Schmutz, G.; Kaiser, R.; Rockstroh, J.K. Safety, efficacy and development of resistance under the new protease inhibitor lopinavir/ritonavir: 48-week results. *Infection* **2004**, *32*, 82-88, doi:10.1007/s15010-004-3059-3.
85. Badiou, S.; De Boever, C.M.; Dupuy, A.M.; Baillat, V.; Cristol, J.P.; Reynes, J. Small dense LDL and atherogenic lipid profile in HIV-positive adults: influence of lopinavir/ritonavir-containing regimen. *AIDS* **2003**, *17*, 772-774, doi:10.1097/00002030-200303280-00023.
86. Montes, M.L.; Pulido, F.; Barros, C.; Condes, E.; Rubio, R.; Cepeda, C.; Dronda, F.; Antela, A.; Sanz, J.; Navas, E.; et al. Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors. *J Antimicrob Chemother* **2005**, *55*, 800-804, doi:10.1093/jac/dki063.
87. Gutierrez, F.; Padilla, S.; Navarro, A.; Masia, M.; Hernandez, I.; Ramos, J.; Esteban, A.; Martin-Hidalgo, A. Lopinavir plasma concentrations and changes in lipid levels during salvage therapy with lopinavir/ritonavir-containing regimens. *J Acquir Immune Defic Syndr* **2003**, *33*, 594-600, doi:10.1097/00126334-200308150-00007.
88. Torti, C.; Quiros-Roldan, E.; Regazzi-Bonora, M.; De Luca, A.; Lo Caputo, S.; Di Giambenedetto, S.; Patroni, A.; Villani, P.; Micheli, V.; Carosi, G.; et al. Lipid abnormalities in HIV-infected patients are not correlated with lopinavir plasma concentrations. *J Acquir Immune Defic Syndr* **2004**, *35*, 324-326, doi:10.1097/00126334-200403010-00017.
89. Dube, M.P.; Qian, D.; Edmondson-Melancon, H.; Sattler, F.R.; Goodwin, D.; Martinez, C.; Williams, V.; Johnson, D.; Buchanan, T.A. Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir-based antiretroviral therapy. *Clin Infect Dis* **2002**, *35*, 475-481, doi:10.1086/341489.
90. Fisac, C.; Virgili, N.; Ferrer, E.; Barbera, M.J.; Fumero, E.; Vilarasau, C.; Podzamczer, D. A comparison of the effects of nevirapine and nelfinavir on metabolism and body habitus in antiretroviral-naive human immunodeficiency virus-infected patients: a randomized controlled study. *J Clin Endocrinol Metab* **2003**, *88*, 5186-5192, doi:10.1210/jc.2002-021830.
91. Squires, K.; Lazzarin, A.; Gatell, J.M.; Powderly, W.G.; Pokrovskiy, V.; Delfraissy, J.F.; Jemsek, J.; Rivero, A.; Rozenbaum, W.; Schrader, S.; et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr* **2004**, *36*, 1011-1019, doi:10.1097/00126334-200408150-00003.
92. Mobius, U.; Lubach-Ruitman, M.; Castro-Frenzel, B.; Stoll, M.; Esser, S.; Voigt, E.; Christensen, S.; Rump, J.A.; Fatkenheuer, G.; Behrens, G.M.; et al. Switching to atazanavir improves metabolic disorders in antiretroviral-experienced patients with severe hyperlipidemia. *J Acquir Immune Defic Syndr* **2005**, *39*, 174-180.
93. Mills, A.M.; Nelson, M.; Jayaweera, D.; Ruxrungtham, K.; Cassetti, I.; Girard, P.M.; Workman, C.; Dierynck, I.; Sekar, V.; Abeele, C.V.; et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS* **2009**, *23*, 1679-1688, doi:10.1097/QAD.0b013e32832d7350.
94. Clotet, B.; Bellos, N.; Molina, J.M.; Cooper, D.; Goffard, J.C.; Lazzarin, A.; Wohrmann, A.; Katlama, C.; Wilkin, T.; Haubrich, R.; et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* **2007**, *369*, 1169-1178, doi:10.1016/S0140-6736(07)60497-8.
95. Aberg, J.A.; Tebas, P.; Overton, E.T.; Gupta, S.K.; Sax, P.E.; Landay, A.; Falcon, R.; Ryan, R.; De La Rosa, G. Metabolic effects of darunavir/ritonavir versus atazanavir/ritonavir in treatment-naive, HIV type 1-infected subjects over 48 weeks. *AIDS Res Hum Retroviruses* **2012**, *28*, 1184-1195, doi:10.1089/aid.2011.0327.
96. Caron, M.; Auclair, M.; Lagathu, C.; Lombes, A.; Walker, U.A.; Kornprobst, M.; Capeau, J. The HIV-1 nucleoside reverse transcriptase inhibitors stavudine and zidovudine alter adipocyte functions in vitro. *AIDS* **2004**, *18*, 2127-2136, doi:10.1097/00002030-200411050-00004.
97. Kakuda, T.N. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* **2000**, *22*, 685-708, doi:10.1016/S0149-2918(00)90004-3.
98. Maagaard, A.; Kvale, D. Long term adverse effects related to nucleoside reverse transcriptase inhibitors: clinical impact of mitochondrial toxicity. *Scand J Infect Dis* **2009**, *41*, 808-817, doi:10.3109/00365540903186181.
99. Johnson, A.A.; Ray, A.S.; Hanes, J.; Suo, Z.; Colacino, J.M.; Anderson, K.S.; Johnson, K.A. Toxicity of antiviral nucleoside analogs and the human mitochondrial DNA polymerase. *J Biol Chem* **2001**, *276*, 40847-40857, doi:10.1074/jbc.M106743200.
100. Zaera, M.G.; Miro, O.; Pedrol, E.; Soler, A.; Picon, M.; Cardellach, F.; Casademont, J.; Nunes, V. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. *AIDS* **2001**, *15*, 1643-1651, doi:10.1097/00002030-200109070-00006.

101. Blas-Garcia, A.; Apostolova, N.; Ballesteros, D.; Monleon, D.; Morales, J.M.; Rocha, M.; Victor, V.M.; Esplugues, J.V. Inhibition of mitochondrial function by efavirenz increases lipid content in hepatic cells. *Hepatology* **2010**, *52*, 115-125, doi:10.1002/hep.23647.
102. Cote, H.C. Possible ways nucleoside analogues can affect mitochondrial DNA content and gene expression during HIV therapy. *Antivir Ther* **2005**, *10 Suppl 2*, M3-11.
103. Mallal, S.A.; John, M.; Moore, C.B.; James, I.R.; McKinnon, E.J. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* **2000**, *14*, 1309-1316, doi:10.1097/00002030-200007070-00002.
104. Shikuma, C.M.; Hu, N.; Milne, C.; Yost, F.; Waslien, C.; Shimizu, S.; Shiramizu, B. Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. *AIDS* **2001**, *15*, 1801-1809, doi:10.1097/00002030-200109280-00009.
105. Cote, H.C.; Brumme, Z.L.; Craib, K.J.; Alexander, C.S.; Wynhoven, B.; Ting, L.; Wong, H.; Harris, M.; Harrigan, P.R.; O'Shaughnessy, M.V.; et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med* **2002**, *346*, 811-820, doi:10.1056/NEJMoa012035.
106. Walker, U.A.; Setzer, B.; Venhoff, N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. *AIDS* **2002**, *16*, 2165-2173, doi:10.1097/00002030-200211080-00009.
107. Llibre, J.M.; Domingo, P.; Palacios, R.; Santos, J.; Perez-Elias, M.J.; Sanchez-de la Rosa, R.; Miralles, C.; Antela, A.; Moreno, S.; Lipo-Rec Study, G. Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. *AIDS* **2006**, *20*, 1407-1414, doi:10.1097/01.aids.0000233574.49220.de.
108. Milinkovic, A.; Martinez, E.; Lopez, S.; de Lazzari, E.; Miro, O.; Vidal, S.; Blanco, J.L.; Garrabou, G.; Laguno, M.; Arnaiz, J.A.; et al. The impact of reducing stavudine dose versus switching to tenofovir on plasma lipids, body composition and mitochondrial function in HIV-infected patients. *Antivir Ther* **2007**, *12*, 407-415.
109. Lundgren, J.D.; Battegay, M.; Behrens, G.; De Wit, S.; Guaraldi, G.; Katlama, C.; Martinez, E.; Nair, D.; Powderly, W.G.; Reiss, P.; et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med* **2008**, *9*, 72-81, doi:10.1111/j.1468-1293.2007.00534.x.
110. Sun, L.Q.; Liu, J.Y.; He, Y.; Zhou, Y.; Xu, L.M.; Zhang, L.K.; Zhao, F.; Liu, X.N.; Song, Y.; Cao, T.Z.; et al. Evolution of blood lipids and risk factors of dyslipidemia among people living with human immunodeficiency virus who had received first-line antiretroviral regimens for 3 years in Shenzhen. *Chin Med J (Engl)* **2020**, *133*, 2808-2815, doi:10.1097/CM9.0000000000001245.
111. Carr, A.; Workman, C.; Smith, D.E.; Hoy, J.; Hudson, J.; Doong, N.; Martin, A.; Amin, J.; Freund, J.; Law, M.; et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA* **2002**, *288*, 207-215, doi:10.1001/jama.288.2.207.
112. Grant, P.M.; Tierney, C.; Budhathoki, C.; Daar, E.S.; Sax, P.E.; Collier, A.C.; Fischl, M.A.; Zolopa, A.R.; Balamane, M.; Katzenstein, D. Early virologic response to abacavir/lamivudine and tenofovir/emtricitabine during ACTG A5202. *HIV Clin Trials* **2013**, *14*, 284-291, doi:10.1310/hct1406-284.
113. Jaschinski, N.; Greenberg, L.; Neesgaard, B.; Miro, J.M.; Grabmeier-Pfistershammer, K.; Wandeler, G.; Smith, C.; De Wit, S.; Wit, F.; Pelchen-Matthews, A.; et al. Recent abacavir use and incident cardiovascular disease in contemporary-treated people with HIV. *AIDS* **2023**, *37*, 467-475, doi:10.1097/QAD.0000000000003373.
114. Martinez-Sanz, J.; Serrano-Villar, S.; Muriel, A.; Garcia Fraile, L.J.; Orviz, E.; Mena de Cea, A.; Campins, A.A.; Moreno, S. Metabolic-Related Outcomes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Adults With Human Immunodeficiency Virus (HIV): A Multicenter Prospective Cohort Study. *Clin Infect Dis* **2023**, *76*, e652-e660, doi:10.1093/cid/ciac621.
115. Moschopoulos, C.D.; Protopapas, K.; Thomas, K.; Kavatha, D.; Papadopoulos, A.; Antoniadou, A. Switching from Tenofovir Disoproxil to Tenofovir Alafenamide Fumarate: Impact on Cardiovascular Risk and Lipid Profile in People Living with HIV, an Observational Study. *AIDS Res Hum Retroviruses* **2023**, *39*, 68-75, doi:10.1089/AID.2022.0086.
116. Friis-Moller, N.; Thiebaut, R.; Reiss, P.; Weber, R.; Monforte, A.D.; De Wit, S.; El-Sadr, W.; Fontas, E.; Worm, S.; Kirk, O.; et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil* **2010**, *17*, 491-501, doi:10.1097/HJR.0b013e328336a150.
117. van der Valk, M.; Kastelein, J.J.; Murphy, R.L.; van Leth, F.; Katlama, C.; Horban, A.; Glesby, M.; Behrens, G.; Clotet, B.; Stellato, R.K.; et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* **2001**, *15*, 2407-2414, doi:10.1097/00002030-200112070-00008.
118. Apostolova, N.; Blas-Garcia, A.; Esplugues, J.V. Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol-gamma inhibition. *Trends Pharmacol Sci* **2011**, *32*, 715-725, doi:10.1016/j.tips.2011.07.007.
119. Apostolova, N.; Gomez-Sucerquia, L.J.; Moran, A.; Alvarez, A.; Blas-Garcia, A.; Esplugues, J.V. Enhanced oxidative stress and increased mitochondrial mass during efavirenz-induced apoptosis in human hepatic cells. *Br J Pharmacol* **2010**, *160*, 2069-2084, doi:10.1111/j.1476-5381.2010.00866.x.

120. Gwag, T.; Meng, Z.; Sui, Y.; Helsley, R.N.; Park, S.H.; Wang, S.; Greenberg, R.N.; Zhou, C. Non-nucleoside reverse transcriptase inhibitor efavirenz activates PXR to induce hypercholesterolemia and hepatic steatosis. *J Hepatol* **2019**, *70*, 930-940, doi:10.1016/j.jhep.2018.12.038.
121. Williams, P.; Wu, J.; Cohn, S.; Koletar, S.; McCutchan, J.; Murphy, R.; Currier, J.; Team, A.C.T.G.S. Improvement in lipid profiles over 6 years of follow-up in adults with AIDS and immune reconstitution. *HIV Med* **2009**, *10*, 290-301, doi:10.1111/j.1468-1293.2008.00685.x.
122. Podzamczer, D.; Andrade-Villanueva, J.; Clotet, B.; Taylor, S.; Rockstroh, J.K.; Reiss, P.; Domingo, P.; Gellermann, H.J.; de Rossi, L.; Cairns, V.; et al. Lipid profiles for nevirapine vs. atazanavir/ritonavir, both combined with tenofovir disoproxil fumarate and emtricitabine over 48 weeks, in treatment-naive HIV-1-infected patients (the ARTEN study). *HIV Med* **2011**, *12*, 374-382, doi:10.1111/j.1468-1293.2011.00917.x.
123. Haubrich, R.H.; Riddler, S.A.; DiRienzo, A.G.; Komarow, L.; Powderly, W.G.; Klingman, K.; Garren, K.W.; Butcher, D.L.; Rooney, J.F.; Haas, D.W.; et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS* **2009**, *23*, 1109-1118, doi:10.1097/QAD.0b013e32832b4377.
124. van Leth, F.; Phanuphak, P.; Stroes, E.; Gazzard, B.; Cahn, P.; Raffi, F.; Wood, R.; Bloch, M.; Katlama, C.; Kastelein, J.J.; et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. *PLoS Med* **2004**, *1*, e19, doi:10.1371/journal.pmed.0010019.
125. Taramasso, L.; Tatarelli, P.; Ricci, E.; Madeddu, G.; Menzaghi, B.; Squillace, N.; De Socio, G.V.; Martinelli, C.; Gulminetti, R.; Maggi, P.; et al. Improvement of lipid profile after switching from efavirenz or ritonavir-boosted protease inhibitors to rilpivirine or once-daily integrase inhibitors: results from a large observational cohort study (SCOLTA). *BMC Infect Dis* **2018**, *18*, 357, doi:10.1186/s12879-018-3268-5.
126. Rokx, C.; Verbon, A.; Rijnders, B.J. Short communication: Lipids and cardiovascular risk after switching HIV-1 patients on nevirapine and emtricitabine/tenofovir-DF to rilpivirine/emtricitabine/tenofovir-DF. *AIDS Res Hum Retroviruses* **2015**, *31*, 363-367, doi:10.1089/AID.2014.0278.
127. MacInnes, A.; Lazzarin, A.; Di Perri, G.; Sierra-Madero, J.G.; Aberg, J.; Heera, J.; Rajicic, N.; Goodrich, J.; Mayer, H.; Valdez, H. Maraviroc can improve lipid profiles in dyslipidemic patients with HIV: results from the MERIT trial. *HIV Clin Trials* **2011**, *12*, 24-36, doi:10.1310/hct1201-24.
128. Valenzuela-Rodriguez, G.; Diaz-Arocutipa, C.; Collins, J.A.; Hernandez, A.V. Weight and Metabolic Outcomes in Naive HIV Patients Treated with Integrase Inhibitor-Based Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *J Clin Med* **2023**, *12*, doi:10.3390/jcm12113644.
129. Cardoso-Neto, E.C.; Netto, E.M.; Brites, C. Weight gain in patients starting Dolutegravir-based ART according to baseline CD4 count after 48 weeks of follow up. *Braz J Infect Dis* **2023**, *27*, 102807, doi:10.1016/j.bjid.2023.102807.
130. Sax, P.E.; Erlandson, K.M.; Lake, J.E.; McComsey, G.A.; Orkin, C.; Esser, S.; Brown, T.T.; Rockstroh, J.K.; Wei, X.; Carter, C.C.; et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. *Clin Infect Dis* **2020**, *71*, 1379-1389, doi:10.1093/cid/ciz999.
131. Bourgeois, C.; Gorwood, J.; Olivo, A.; Le Pelletier, L.; Capeau, J.; Lambotte, O.; Bereziat, V.; Lagathu, C. Contribution of Adipose Tissue to the Chronic Immune Activation and Inflammation Associated With HIV Infection and Its Treatment. *Front Immunol* **2021**, *12*, 670566, doi:10.3389/fimmu.2021.670566.
132. Lake, J.E. The Fat of the Matter: Obesity and Visceral Adiposity in Treated HIV Infection. *Curr HIV/AIDS Rep* **2017**, *14*, 211-219, doi:10.1007/s11904-017-0368-6.
133. Couturier, J.; Winchester, L.C.; Suliburk, J.W.; Wilkerson, G.K.; Podany, A.T.; Agarwal, N.; Xuan Chua, C.Y.; Nehete, P.N.; Nehete, B.P.; Grattoni, A.; et al. Adipocytes impair efficacy of antiretroviral therapy. *Antiviral Res* **2018**, *154*, 140-148, doi:10.1016/j.antiviral.2018.04.002.
134. Gorwood, J.; Bourgeois, C.; Pourcher, V.; Pourcher, G.; Charlotte, F.; Mantecon, M.; Rose, C.; Morichon, R.; Atlan, M.; Le Grand, R.; et al. The Integrase Inhibitors Dolutegravir and Raltegravir Exert Proadipogenic and Profibrotic Effects and Induce Insulin Resistance in Human/Simian Adipose Tissue and Human Adipocytes. *Clin Infect Dis* **2020**, *71*, e549-e560, doi:10.1093/cid/ciaa259.
135. Katlama, C.; Assoumou, L.; Valantin, M.A.; Soulie, C.; Martinez, E.; Beniguel, L.; Bouchaud, O.; Raffi, F.; Molina, J.M.; Fellahi, S.; et al. Dual therapy combining raltegravir with etravirine maintains a high level of viral suppression over 96 weeks in long-term experienced HIV-infected individuals over 45 years on a PI-based regimen: results from the Phase II ANRS 163 ETRAL study. *J Antimicrob Chemother* **2019**, *74*, 2742-2751, doi:10.1093/jac/dkz224.
136. Dirajlal-Fargo, S.; Moser, C.; Brown, T.T.; Kelesidis, T.; Dube, M.P.; Stein, J.H.; Currier, J.; McComsey, G.A. Changes in Insulin Resistance After Initiation of Raltegravir or Protease Inhibitors With Tenofovir-Emtricitabine: AIDS Clinical Trials Group A5260s. *Open Forum Infect Dis* **2016**, *3*, ofw174, doi:10.1093/ofid/ofw174.
137. Ofotokun, I.; Na, L.H.; Landovitz, R.J.; Ribaudo, H.J.; McComsey, G.A.; Godfrey, C.; Aweeka, F.; Cohn, S.E.; Sagar, M.; Kuritzkes, D.R.; et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis* **2015**, *60*, 1842-1851, doi:10.1093/cid/civ193.

138. Pantazis, N.; Papastamopoulos, V.; Antoniadou, A.; Adamis, G.; Paparizos, V.; Metallidis, S.; Sambatakou, H.; Psichogiou, M.; Chini, M.; Chrysos, G.; et al. Changes in Body Mass Index after Initiation of Antiretroviral Treatment: Differences by Class of Core Drug. *Viruses* **2022**, *14*, doi:10.3390/v14081677.
139. The, R.S.G. Incidence of dyslipidemia in people with HIV who are treated with integrase inhibitors versus other antiretroviral agents. *AIDS* **2021**, *35*, 869-882, doi:10.1097/QAD.0000000000002811.
140. Baldin, G.; Ciccullo, A.; Lombardi, F.; D'Angelillo, A.; Dusina, A.; Emiliozzi, A.; Farinacci, D.; Moschese, D.; Picarelli, C.; Borghetti, A.; et al. Short Communication: Comparing Lamivudine+Dolutegravir and Bictegravir/Emtricitabine/Tenofovir Alafenamide as Switch Strategies: Preliminary Results from Clinical Practice. *AIDS Res Hum Retroviruses* **2021**, *37*, 429-432, doi:10.1089/AID.2020.0219.
141. Adachi, E.; Saito, M.; Otani, A.; Koga, M.; Yotsuyanagi, H. Brief communications: changes in inflammatory biomarkers and lipid profiles after switching to long-acting cabotegravir plus rilpivirine. *AIDS Res Ther* **2024**, *21*, 1, doi:10.1186/s12981-023-00590-4.
142. Achhra, A.C.; Lyass, A.; Borowsky, L.; Bogorodskaya, M.; Plutzky, J.; Massaro, J.M.; D'Agostino, R.B., Sr.; Triant, V.A. Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations. *Curr HIV/AIDS Rep* **2021**, *18*, 271-279, doi:10.1007/s11904-021-00567-w.
143. Triant, V.A.; Perez, J.; Regan, S.; Massaro, J.M.; Meigs, J.B.; Grinspoon, S.K.; D'Agostino, R.B., Sr. Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. *Circulation* **2018**, *137*, 2203-2214, doi:10.1161/CIRCULATIONAHA.117.028975.
144. Schachter, M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* **2005**, *19*, 117-125, doi:10.1111/j.1472-8206.2004.00299.x.
145. Harrington, R.A. Statins-Almost 30 Years of Use in the United States and Still Not Quite There. *JAMA Cardiol* **2017**, *2*, 66, doi:10.1001/jamacardio.2016.4709.
146. Moore, R.D.; Bartlett, J.G.; Gallant, J.E. Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients. *PLoS One* **2011**, *6*, e21843, doi:10.1371/journal.pone.0021843.
147. Li, Y.; Wang, Z.; Xia, H.; Zhang, J. Influence of Statin Therapy on the Incidence of Cardiovascular Events, Cancer, and All-Cause Mortality in People Living With HIV: A Meta-Analysis. *Front Med (Lausanne)* **2021**, *8*, 769740, doi:10.3389/fmed.2021.769740.
148. Schonbeck, U.; Libby, P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation* **2004**, *109*, II18-26, doi:10.1161/01.CIR.0000129505.34151.23.
149. Phipps, R.P.; Blumberg, N. Statin islands and PPAR ligands in platelets. *Arterioscler Thromb Vasc Biol* **2009**, *29*, 620-621, doi:10.1161/ATVBAHA.109.184648.
150. Wolfrum, S.; Jensen, K.S.; Liao, J.K. Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* **2003**, *23*, 729-736, doi:10.1161/01.ATV.0000063385.12476.A7.
151. Laufs, U.; Liao, J.K. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. *J Biol Chem* **1998**, *273*, 24266-24271, doi:10.1074/jbc.273.37.24266.
152. Loppnow, H.; Zhang, L.; Buerke, M.; Lautenschlager, M.; Chen, L.; Frister, A.; Schlitt, A.; Luther, T.; Song, N.; Hofmann, B.; et al. Statins potently reduce the cytokine-mediated IL-6 release in SMC/MNC cocultures. *J Cell Mol Med* **2011**, *15*, 994-1004, doi:10.1111/j.1582-4934.2010.01036.x.
153. Kosmidou, I.; Moore, J.P.; Weber, M.; Searles, C.D. Statin treatment and 3' polyadenylation of eNOS mRNA. *Arterioscler Thromb Vasc Biol* **2007**, *27*, 2642-2649, doi:10.1161/ATVBAHA.107.154492.
154. Arevalo-Lorido, J.C. Clinical relevance for lowering C-reactive protein with statins. *Ann Med* **2016**, *48*, 516-524, doi:10.1080/07853890.2016.1197413.
155. Tani, S.; Takahashi, A.; Nagao, K.; Hirayama, A. Contribution of apolipoprotein A-I to the reduction in high-sensitivity C-reactive protein levels by different statins: comparative study of pitavastatin and atorvastatin. *Heart Vessels* **2015**, *30*, 762-770, doi:10.1007/s00380-014-0554-z.
156. Greenwood, J.; Steinman, L.; Zamvil, S.S. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol* **2006**, *6*, 358-370, doi:10.1038/nri1839.
157. Zivkovic, S.; Maric, G.; Cvetinovic, N.; Lepojevic-Stefanovic, D.; Bozic Cvijan, B. Anti-Inflammatory Effects of Lipid-Lowering Drugs and Supplements-A Narrative Review. *Nutrients* **2023**, *15*, doi:10.3390/nu15061517.
158. Nixon, D.E.; Bosch, R.J.; Chan, E.S.; Funderburg, N.T.; Hodder, S.; Lake, J.E.; Lederman, M.M.; Klingman, K.L.; Aberg, J.A.; Team, A.C.T.G.S.A. Effects of atorvastatin on biomarkers of immune activation, inflammation, and lipids in virologically suppressed, human immunodeficiency virus-1-infected individuals with low-density lipoprotein cholesterol <130 mg/dL (AIDS Clinical Trials Group Study A5275). *J Clin Lipidol* **2017**, *11*, 61-69, doi:10.1016/j.jacl.2016.09.017.
159. Calza, L.; Colangeli, V.; Borderi, M.; Beci, G.; Esposito, F.; Bon, I.; Re, M.C.; Viale, P. Rosuvastatin decreases serum inflammatory markers and slows atherosclerosis progression rate in treated HIV-infected patients with metabolic syndrome. *Infect Dis (Lond)* **2021**, *53*, 81-88, doi:10.1080/23744235.2020.1823468.
160. Mora, S.; Glynn, R.J.; Hsia, J.; MacFadyen, J.G.; Genest, J.; Ridker, P.M. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating

Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation* **2010**, *121*, 1069-1077, doi:10.1161/CIRCULATIONAHA.109.906479.
161. Funderburg, N.T.; Jiang, Y.; Debanne, S.M.; Storer, N.; Labbato, D.; Clagett, B.; Robinson, J.; Lederman, M.M.; McComsey, G.A. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis* **2014**, *58*, 588-595, doi:10.1093/cid/cit748.
162. Cholesterol Treatment Trialists, C.; Baigent, C.; Blackwell, L.; Emberson, J.; Holland, L.E.; Reith, C.; Bhala, N.; Peto, R.; Barnes, E.H.; Keech, A.; et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **2010**, *376*, 1670-1681, doi:10.1016/S0140-6736(10)61350-5.
163. Calza, L.; Manfredi, R.; Colangeli, V.; Pocaterra, D.; Pavoni, M.; Chiodo, F. Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolaemia in HIV-infected patients receiving protease inhibitors. *Curr HIV Res* **2008**, *6*, 572-578, doi:10.2174/157016208786501481.
164. Lo, J.; Lu, M.T.; Ihenachor, E.J.; Wei, J.; Looby, S.E.; Fitch, K.V.; Oh, J.; Zimmerman, C.O.; Hwang, J.; Abbara, S.; et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV* **2015**, *2*, e52-63, doi:10.1016/S2352-3018(14)00032-0.
165. Rahman, A.P.; Eaton, S.A.; Nguyen, S.T.; Bain, A.M.; Payne, K.D.; Bedimo, R.; Busti, A.J. Safety and efficacy of simvastatin for the treatment of dyslipidemia in human immunodeficiency virus-infected patients receiving efavirenz-based highly active antiretroviral therapy. *Pharmacotherapy* **2008**, *28*, 913-919, doi:10.1592/phco.28.7.913.
166. Sabin, C.A.; Yee, T.T.; Devereux, H.; Griffioen, A.; Loveday, C.; Phillips, A.N.; Lee, C.A. Two decades of HIV infection in a cohort of haemophilic individuals: clinical outcomes and response to highly active antiretroviral therapy. *AIDS* **2000**, *14*, 1001-1007, doi:10.1097/00002030-200005260-00012.
167. Aberg, J.A.; Sponseller, C.A.; Ward, D.J.; Kryzhanovski, V.A.; Campbell, S.E.; Thompson, M.A. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. *Lancet HIV* **2017**, *4*, e284-e294, doi:10.1016/S2352-3018(17)30075-9.
168. Grinspoon, S.K.; Fitch, K.V.; Zanni, M.V.; Fichtenbaum, C.J.; Umbleja, T.; Aberg, J.A.; Overton, E.T.; Malvestutto, C.D.; Bloomfield, G.S.; Currier, J.S.; et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. *N Engl J Med* **2023**, *389*, 687-699, doi:10.1056/NEJMoa2304146.
169. Myerson, M.; Malvestutto, C.; Aberg, J.A. Management of lipid disorders in patients living with HIV. *J Clin Pharmacol* **2015**, *55*, 957-974, doi:10.1002/jcph.473.
170. Gervasoni, C.; Riva, A.; Rizzardini, G.; Clementi, E.; Galli, M.; Cattaneo, D. Potential association between rosuvastatin use and high atazanavir trough concentrations in ritonavir-treated HIV-infected patients. *Antivir Ther* **2015**, *20*, 449-451, doi:10.3851/IMP2872.
171. Chauvin, B.; Drouot, S.; Barrail-Tran, A.; Taburet, A.M. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. *Clin Pharmacokinet* **2013**, *52*, 815-831, doi:10.1007/s40262-013-0075-4.
172. Ieiri, I.; Tsunemitsu, S.; Maeda, K.; Ando, Y.; Izumi, N.; Kimura, M.; Yamane, N.; Okuzono, T.; Morishita, M.; Kotani, N.; et al. Mechanisms of pharmacokinetic enhancement between ritonavir and saquinavir; micro/small dosing tests using midazolam (CYP3A4), fexofenadine (p-glycoprotein), and pravastatin (OATP1B1) as probe drugs. *J Clin Pharmacol* **2013**, *53*, 654-661, doi:10.1002/jcph.62.
173. Aberg, J.A.; Rosenkranz, S.L.; Fichtenbaum, C.J.; Alston, B.L.; Brobst, S.W.; Segal, Y.; Gerber, J.G.; team, A.A. Pharmacokinetic interaction between nelfinavir and pravastatin in HIV-seronegative volunteers: ACTG Study A5108. *AIDS* **2006**, *20*, 725-729, doi:10.1097/01.aids.0000216373.53819.92.
174. Fichtenbaum, C.J.; Gerber, J.G.; Rosenkranz, S.L.; Segal, Y.; Aberg, J.A.; Blaschke, T.; Alston, B.; Fang, F.; Kosel, B.; Aweeka, F.; et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* **2002**, *16*, 569-577, doi:10.1097/00002030-200203080-00008.
175. Hare, C.B.; Vu, M.P.; Grunfeld, C.; Lampiris, H.W. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis* **2002**, *35*, e111-112, doi:10.1086/344179.
176. Courlet, P.; Decosterd, L.A.; Alves Saldanha, S.; Cavassini, M.; Stader, F.; Stoeckle, M.; Buclin, T.; Marzolini, C.; Csajka, C.; Guidi, M.; et al. Influence of Drug-Drug Interactions on the Pharmacokinetics of Atorvastatin and Its Major Active Metabolite ortho-OH-Atorvastatin in Aging People Living with HIV. *Clin Pharmacokinet* **2020**, *59*, 1037-1048, doi:10.1007/s40262-020-00876-0.
177. Gibert, C.L. Treatment Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents: An Update. *Fed Pract* **2016**, *33*, 31S-36S.
178. Custodio, J.M.; Wang, H.; Hao, J.; Lepist, E.I.; Ray, A.S.; Andrews, J.; Ling, K.H.; Cheng, A.; Kearney, B.P.; Ramanathan, S. Pharmacokinetics of cobicistat boosted-elvitegravir administered in combination with rosuvastatin. *J Clin Pharmacol* **2014**, *54*, 649-656, doi:10.1002/jcph.256.

179. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* **2020**, *41*, 111-188, doi:10.1093/eurheartj/ehz455.
180. Nirmala, N.; Avendano, E.E.; Morin, R.A. Effectiveness of ezetimibe in human immunodeficiency virus patients treated for hyperlipidaemia: a systematic review and meta-analysis. *Infect Dis (Lond)* **2022**, *54*, 99-109, doi:10.1080/23744235.2021.1982140.
181. Saeedi, R.; Johns, K.; Frohlich, J.; Bennett, M.T.; Bondy, G. Lipid lowering efficacy and safety of Ezetimibe combined with rosuvastatin compared with titrating rosuvastatin monotherapy in HIV-positive patients. *Lipids Health Dis* **2015**, *14*, 57, doi:10.1186/s12944-015-0054-x.
182. Alvarez-Sala, L.A.; Cachofeiro, V.; Masana, L.; Suarez, C.; Pinilla, B.; Plana, N.; Trias, F.; Moreno, M.A.; Gambus, G.; Lahera, V.; et al. Effects of fluvastatin extended-release (80 mg) alone and in combination with ezetimibe (10 mg) on low-density lipoprotein cholesterol and inflammatory parameters in patients with primary hypercholesterolemia: a 12-week, multicenter, randomized, open-label, parallel-group study. *Clin Ther* **2008**, *30*, 84-97, doi:10.1016/j.linthera.2008.01.013.
183. Ghanim, H.; Green, K.; Abuaysheh, S.; Patel, R.; Batra, M.; Chaudhuri, A.; Makdissi, A.; Kuhadiya, N.D.; Dandona, P. Ezetimibe and simvastatin combination inhibits and reverses the pro-inflammatory and pro-atherogenic effects of cream in obese patients. *Atherosclerosis* **2017**, *263*, 278-286, doi:10.1016/j.atherosclerosis.2017.06.010.
184. Kunz, H.E.; Hart, C.R.; Gries, K.J.; Parvizi, M.; Laurenti, M.; Dalla Man, C.; Moore, N.; Zhang, X.; Ryan, Z.; Polley, E.C.; et al. Adipose tissue macrophage populations and inflammation are associated with systemic inflammation and insulin resistance in obesity. *Am J Physiol Endocrinol Metab* **2021**, *321*, E105-E121, doi:10.1152/ajpendo.00070.2021.
185. Qin, L.; Yang, Y.B.; Yang, Y.X.; Zhu, N.; Li, S.X.; Liao, D.F.; Zheng, X.L. Anti-inflammatory activity of ezetimibe by regulating NF-kappaB/MAPK pathway in THP-1 macrophages. *Pharmacology* **2014**, *93*, 69-75, doi:10.1159/000357953.
186. Scherer, D.J.; Nelson, A.J.; Psaltis, P.J.; Nicholls, S.J. Targeting low-density lipoprotein cholesterol with PCSK9 inhibitors. *Intern Med J* **2017**, *47*, 856-865, doi:10.1111/imj.13451.
187. Sabatine, M.S.; Giugliano, R.P.; Wiviott, S.D.; Raal, F.J.; Blom, D.J.; Robinson, J.; Ballantyne, C.M.; Somaratne, R.; Legg, J.; Wasserman, S.M.; et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* **2015**, *372*, 1500-1509, doi:10.1056/NEJMoa1500858.
188. Sabatine, M.S.; Giugliano, R.P.; Keech, A.C.; Honarpour, N.; Wiviott, S.D.; Murphy, S.A.; Kuder, J.F.; Wang, H.; Liu, T.; Wasserman, S.M.; et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* **2017**, *376*, 1713-1722, doi:10.1056/NEJMoa1615664.
189. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* **2018**, *379*, 2097-2107, doi:10.1056/NEJMoa1801174.
190. Leucker, T.M.; Gerstenblith, G.; Schar, M.; Brown, T.T.; Jones, S.R.; Afework, Y.; Weiss, R.G.; Hays, A.G. Evolocumab, a PCSK9-Monoclonal Antibody, Rapidly Reverses Coronary Artery Endothelial Dysfunction in People Living With HIV and People With Dyslipidemia. *J Am Heart Assoc* **2020**, *9*, e016263, doi:10.1161/JAHA.120.016263.
191. Boccara, F.; Caramelli, B.; Calmy, A.; Kumar, P.; Lopez, J.A.G.; Bray, S.; Cyrille, M.; Rosenson, R.S.; investigators of the, B.s. Long-term effects of evolocumab in participants with HIV and dyslipidemia: results from the open-label extension period. *AIDS* **2022**, *36*, 675-682, doi:10.1097/QAD.0000000000003175.
192. Bernelot Moens, S.J.; Neele, A.E.; Kroon, J.; van der Valk, F.M.; Van den Bossche, J.; Hoeksema, M.A.; Hoogeveen, R.M.; Schnitzler, J.G.; Baccara-Dinet, M.T.; Manvelian, G.; et al. PCSK9 monoclonal antibodies reverse the pro-inflammatory profile of monocytes in familial hypercholesterolaemia. *Eur Heart J* **2017**, *38*, 1584-1593, doi:10.1093/eurheartj/ehx002.
193. Tang, Z.; Jiang, L.; Peng, J.; Ren, Z.; Wei, D.; Wu, C.; Pan, L.; Jiang, Z.; Liu, L. PCSK9 siRNA suppresses the inflammatory response induced by oxLDL through inhibition of NF-kappaB activation in THP-1-derived macrophages. *Int J Mol Med* **2012**, *30*, 931-938, doi:10.3892/ijmm.2012.1072.
194. Agha, A.M.; Jones, P.H.; Ballantyne, C.M.; Virani, S.S.; Nambi, V. Greater than expected reduction in low-density lipoprotein-cholesterol (LDL-C) with bempedoic acid in a patient with heterozygous familial hypercholesterolemia (HeFH). *J Clin Lipidol* **2021**, *15*, 649-652, doi:10.1016/j.jacl.2021.07.002.
195. Burke, A.C.; Telford, D.E.; Sutherland, B.G.; Edwards, J.Y.; Sawyez, C.G.; Barrett, P.H.R.; Newton, R.S.; Pickering, J.G.; Huff, M.W. Bempedoic Acid Lowers Low-Density Lipoprotein Cholesterol and Attenuates Atherosclerosis in Low-Density Lipoprotein Receptor-Deficient (LDLR(+/-) and LDLR(-/-)) Yucatan Miniature Pigs. *Arterioscler Thromb Vasc Biol* **2018**, *38*, 1178-1190, doi:10.1161/ATVBAHA.117.310676.
196. Banach, M.; Duell, P.B.; Gotto, A.M., Jr.; Laufs, U.; Leiter, L.A.; Mancini, G.B.J.; Ray, K.K.; Flaim, J.; Ye, Z.; Catapano, A.L. Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. *JAMA Cardiol* **2020**, *5*, 1124-1135, doi:10.1001/jamacardio.2020.2314.

197. Nissen, S.E.; Lincoff, A.M.; Brennan, D.; Ray, K.K.; Mason, D.; Kastelein, J.J.P.; Thompson, P.D.; Libby, P.; Cho, L.; Plutzky, J.; et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med* **2023**, *388*, 1353-1364, doi:10.1056/NEJMoa2215024.
198. Ballantyne, C.M.; Laufs, U.; Ray, K.K.; Leiter, L.A.; Bays, H.E.; Goldberg, A.C.; Stroes, E.S.; MacDougall, D.; Zhao, X.; Catapano, A.L. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol* **2020**, *27*, 593-603, doi:10.1177/2047487319864671.
199. Cicero, A.F.G.; Fogacci, F.; Cincione, I. Evaluating pharmacokinetics of bempedoic acid in the treatment of hypercholesterolemia. *Expert Opin Drug Metab Toxicol* **2021**, *17*, 1031-1038, doi:10.1080/17425255.2021.1951222.
200. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082-e1143, doi:10.1161/CIR.0000000000000625.
201. Montaigne, D.; Butruille, L.; Staels, B. PPAR control of metabolism and cardiovascular functions. *Nat Rev Cardiol* **2021**, *18*, 809-823, doi:10.1038/s41569-021-00569-6.
202. Kytikova, O.Y.; Perelman, J.M.; Novgorodtseva, T.P.; Denisenko, Y.K.; Kolosov, V.P.; Antonyuk, M.V.; Gvozdenko, T.A. Peroxisome Proliferator-Activated Receptors as a Therapeutic Target in Asthma. *PPAR Res* **2020**, *2020*, 8906968, doi:10.1155/2020/8906968.
203. Busse, K.H.; Hadigan, C.; Chairez, C.; Alfaro, R.M.; Formentini, E.; Kovacs, J.A.; Penzak, S.R. Gemfibrozil concentrations are significantly decreased in the presence of lopinavir-ritonavir. *J Acquir Immune Defic Syndr* **2009**, *52*, 235-239, doi:10.1097/QAI.0b013e3181b0610e.
204. Nakagomi-Hagihara, R.; Nakai, D.; Tokui, T.; Abe, T.; Ikeda, T. Gemfibrozil and its glucuronide inhibit the hepatic uptake of pravastatin mediated by OATP1B1. *Xenobiotica* **2007**, *37*, 474-486, doi:10.1080/00498250701278442.
205. Silverberg, M.J.; Leyden, W.; Hurley, L.; Go, A.S.; Quesenberry, C.P., Jr.; Klein, D.; Horberg, M.A. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. *Ann Intern Med* **2009**, *150*, 301-313, doi:10.7326/0003-4819-150-5-200903030-00006.
206. Munoz, M.A.; Liu, W.; Delaney, J.A.; Brown, E.; Mugavero, M.J.; Mathews, W.C.; Napravnik, S.; Willig, J.H.; Eron, J.J.; Hunt, P.W.; et al. Comparative effectiveness of fish oil versus fenofibrate, gemfibrozil, and atorvastatin on lowering triglyceride levels among HIV-infected patients in routine clinical care. *J Acquir Immune Defic Syndr* **2013**, *64*, 254-260, doi:10.1097/QAI.0b013e3182a60e82.
207. Grandi, A.M.; Nicolini, E.; Rizzi, L.; Caputo, S.; Annoni, F.; Cremona, A.M.; Marchesi, C.; Guasti, L.; Maresca, A.M.; Grossi, P. Dyslipidemia in HIV-positive patients: a randomized, controlled, prospective study on ezetimibe+fenofibrate versus pravastatin monotherapy. *J Int AIDS Soc* **2014**, *17*, 19004, doi:10.7448/IAS.17.1.1900419004.
208. Das Pradhan, A.; Glynn, R.J.; Fruchart, J.C.; MacFadyen, J.G.; Zaharris, E.S.; Everett, B.M.; Campbell, S.E.; Oshima, R.; Amarenco, P.; Blom, D.J.; et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N Engl J Med* **2022**, *387*, 1923-1934, doi:10.1056/NEJMoa2210645.
209. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. *J Am Coll Cardiol* **2019**, *73*, 2791-2802, doi:10.1016/j.jacc.2019.02.032.
210. Ridker, P.M.; Rifai, N.; MacFadyen, J.; Glynn, R.J.; Jiao, L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Tardif, J.C.; et al. Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1beta, Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: A REDUCE-IT Biomarker Substudy. *Circulation* **2022**, *146*, 372-379, doi:10.1161/CIRCULATIONAHA.122.059410.
211. Peters, B.S.; Wierzbicki, A.S.; Moyle, G.; Nair, D.; Brockmeyer, N. The effect of a 12-week course of omega-3 polyunsaturated fatty acids on lipid parameters in hypertriglyceridemic adult HIV-infected patients undergoing HAART: a randomized, placebo-controlled pilot trial. *Clin Ther* **2012**, *34*, 67-76, doi:10.1016/j.clinthera.2011.12.001.
212. Gerber, J.G.; Kitch, D.W.; Fichtenbaum, C.J.; Zackin, R.A.; Charles, S.; Hogg, E.; Acosta, E.P.; Connick, E.; Wohl, D.; Kojic, E.M.; et al. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr* **2008**, *47*, 459-466, doi:10.1097/QAI.0b013e31815bace2.
213. Fogacci, F.; Strocchi, E.; Veronesi, M.; Borghi, C.; Cicero, A.F.G. Effect of Omega-3 Polyunsaturated Fatty Acids Treatment on Lipid Pattern of HIV Patients: A Meta-Analysis of Randomized Clinical Trials. *Mar Drugs* **2020**, *18*, doi:10.3390/md18060292.

 doi:10.20944/preprints202403.0075.v1