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Review article

Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review☆

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ABSTRACT

This study reviewed the lipid profile of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients in relation to use of antiretroviral therapy (ART), and its different classes of drugs. A total of 190 articles published in peer-reviewed journals were retrieved from PubMed and LILACS databases; 88 of them met the selection criteria and were included in the review. Patients with HIV/AIDS without ART presented an increase of triglycerides and decreases of total cholesterol, low density lipoprotein (LDL-c), and high density lipoprotein (HDL-c) levels. Distinct ART regimens appear to promote different alterations in lipid metabolism. Protease inhibitors, particularly indinavir and lopinavir, were commonly associated with hypercholesterolemia, high LDL-c, low HDL-c, and hypertriglyceridemia. The protease inhibitor atazanavir is apparently associated with a more advantageous lipid profile. Some nucleoside reverse-transcriptase inhibitors (didanosine, stavudine, and zidovudine) induced lipoatrophy and hypertriglyceridemia, whereas abacavir increased the risk of cardiovascular diseases even in the absence of apparent lipid disorders, and tenofovir resulted in lower levels of cholesterol and triglycerides. Although non-nucleoside reverse-transcriptase inhibitors predisposed to hypertriglyceridemia and hypercholesterolemia, nevirapine was particularly associated with high HDL-c levels, a protective factor against cardiovascular diseases. Therefore, the infection itself, different classes of drugs, and some drugs from the same class of ART appear to exert distinct alterations in lipid metabolism.

Perfil lipídico de pacientes infectados pelo HIV em relação à terapia antirretroviral: uma revisão

Palavras-chave:
Vírus da Imunodeficiência Humana

RESUMO

Este estudo faz uma revisão sobre o perfil lipídico de pacientes com vírus da imunodeficiência humana/síndrome da imunodeficiência adquirida (HIV/AIDS) em relação ao uso da terapia antirretroviral (TARV), e suas diferentes classes de fármacos. Um total de 190 artigos

☆ Study conducted at Faculdade de Saúde Pública da Universidade de São Paulo, São Paulo, SP, Brazil.

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Síndrome da Imunodeficiência Adquirida
Terapia antirretroviral
Terapia antirretroviral de alta potência
Dislipidemia

publicados em revistas indexadas foram selecionados das bases de dados PubMed e LILACS; 88 deles preencheram os critérios de seleção e foram incluídos nesta revisão. Pacientes com HIV/AIDS sem uso de TARV apresentaram aumento de triglicérides e diminuição dos níveis de colesterol total, lipoproteína de baixa densidade (LDL-c) e lipoproteína de alta densidade (HDL-c). Distintos regimes de TARV promoveram diferentes alterações no metabolismo lipídico. Inibidores de protease, particularmente indinavir e lopinavir, foram comumente associados com hipercolesterolemia, aumento de LDL-c, diminuição de HDL-c e hipertrigliceridemia. O inibidor de protease atazanavir aparentemente está associado a menores alterações do perfil lipídico. Alguns inibidores da transcripitase reversa análogos de nucleosídeos (didanosina, estavudina e zidovudina), induziram lipoatrofia e hipertrigliceridemia, enquanto o abacavir aumentou o risco cardiovascular mesmo na ausência de aparentes distúrbios lipídicos, e o tenofovir resultou em menores níveis de colesterol e triglicérides. Embora os inibidores da transcriptase reversa não análogos de nucleosídeos possam predispor a hipertrigliceridemia e hipercolesterolemia, a nevirapina, particularmente, foi associada a maiores níveis de HDL-c, um fator de proteção contra doenças cardiovasculares. Portanto, a própria infecção, diferentes classes de fármacos e alguns fármacos da mesma classe de TARV podem exercer distintas alterações no metabolismo lipídico.

Introduction

Patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) frequently present alterations in lipid metabolism due to infection with HIV itself, including elevated serum concentrations of triglycerides and low levels of total cholesterol.[1] The introduction of antiretroviral therapy (ART) in the mid-1990s led to substantial improvement in the prognosis of HIV/AIDS patients, with a reduction in morbidity and mortality due to opportunistic diseases and consequent improvement of the patient's quality of life.[2–7]

However, there is evidence that ART is associated with lipodystrophy syndrome, a disturbance of lipid metabolism characterized by insulin resistance, dyslipidemia, and fat maldistribution, usually presenting as visceral abdominal obesity and cervical fat pad accumulation (buffalo hump),[2,5,7–9] metabolic bone disease (osteopenia and/or osteoporosis), and lactic acidosis.[5,7,10–12]

ART-associated dyslipidemia is characterized by elevated serum concentrations of total cholesterol, triglycerides, low density lipoprotein (LDL-c), very low-density lipoprotein (VLDL), and apolipoprotein B (apoB), and low levels of high density lipoprotein (HDL-c), constituting an atherogenic lipid profile.[13,14] This lipid changes occurs within three months of initiating ART, and plateau after six to nine months.[15]

The prevalence of dyslipidemia and other risk factors for cardiovascular disease is significant in HIV/AIDS patients receiving ART, ranging from 20% to 80% depending on the study design and population investigated.[8] These lipid alterations were first described in patients who used antiretroviral regimens containing protease inhibitors, but also were later observed in patients who received regimens consisting of nucleoside reverse-transcriptase inhibitors (NRTI) and non-nucleoside reverse-transcriptase inhibitors (NNRTI).[16,17]

In view of the high prevalence of dyslipidemia and the increased risk for cardiovascular diseases among patients with HIV/AIDS, which is a matter of concern for public health, the present review aimed to describe the lipid profile of HIV-infected patients in relation to use of ART, and its different classes of drugs.

Methods

The PubMed (US National Library of Medicine, National Institutes of Health) and LILACS (Literatura Latino-Americana e do Caribe) databases were searched without restrictions on publication year or study design until August 2011. The keywords "HIV" [MESH] OR "Acquired Immunodeficiency Syndrome" [MESH] AND "Dyslipidemias" [MESH] were used for search in the PubMed database, and 169 articles were retrieved. The LILACS database was searched using "HIV and Dislipidemia", and 21 articles were retrieved. Thus, 190 articles were first selected, but one article appeared in both databases; therefore, 189 articles were selected for this review.

All studies investigating the association between lipid alterations in HIV/AIDS patients with or without treatment were identified and included in the review. Case report articles (12 articles from PubMed), articles related to lipid-lowering drugs (8 articles from PubMed), articles whose full text could not be accessed (35 articles from PubMed and five from LILACS), and articles not focusing on lipid alterations in HIV/AIDS patients (39 articles from PubMed and nine from LILACS) were excluded. 75 articles were thus selected from the PubMed database and six articles from the LILACS database. In addition, seven studies were identified in the references of these articles and retrieved for relevance, considering that the articles were useful to describe the possible metabolic mechanisms to explain the lipid alterations of the patients. Therefore, a total of 88 articles were included in the review (Fig. 1).

All the 88 articles were discussed in this review. Tables 1 and 3 presented the results of the original articles (n = 51) included in this search, excluding previously published reviews.

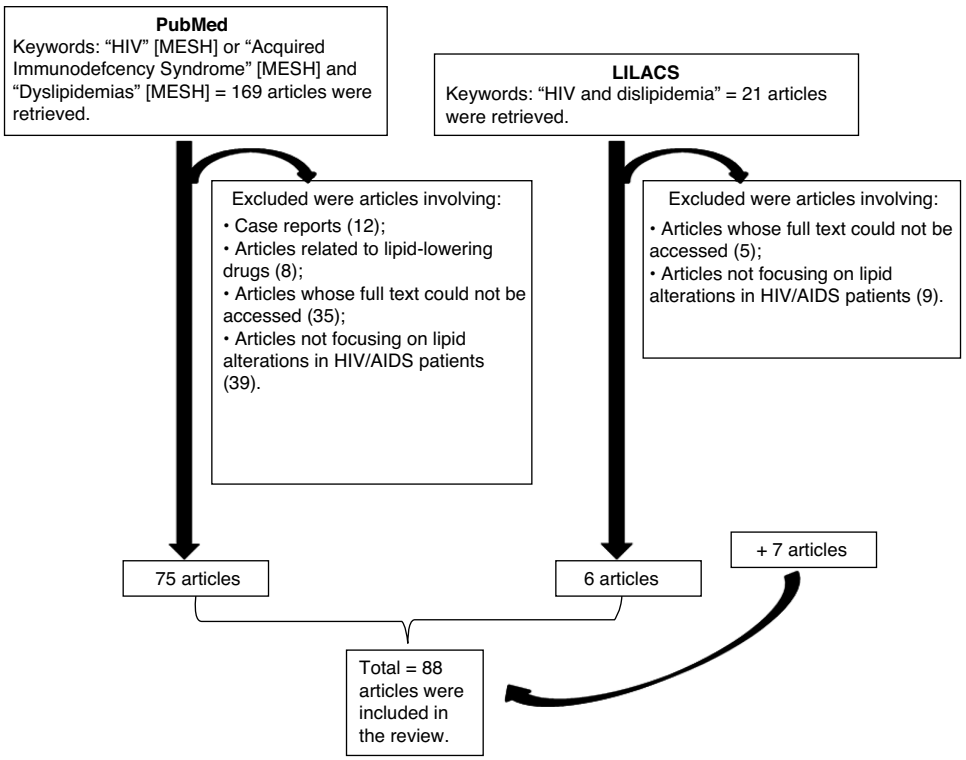

Fig. 1 – Research design.

Results and discussion

HIV/AIDS and lipid alterations

Lipid alterations in patients with HIV/AIDS caused by the infection itself had been reported before the implementation of ART.[1,13] In this respect, serum triglyceride concentrations were higher and the levels of total cholesterol, LDL-c and HDL-c were lower in HIV-seropositive patients receiving no ART when compared to uninfected controls.[1,18,19] These alterations were detected in patients infected with different HIV-1 subtypes.[19]

Low serum concentrations of HDL-c can be used as a marker of chronic inflammatory activity.[20] In a cohort study conducted in Spain, untreated HIV-infected patients presented low HDL-c levels, especially if they had already received antiretroviral therapy in the past.[21] However, HDL-c levels were found to be low even in patients receiving ART presenting adequate viral suppression and immune reconstitution, a finding that suggests that inflammatory activity was not completely controlled.[20]

Table 1 summarizes the results of the original studies (n = 3) that assessed the lipid profile of HIV/AIDS patients without ART.

Possible metabolic mechanisms

Factors that contribute to dyslipidemia in HIV infection are altered cytokine profile, decreased lipid clearance, and increased hepatic synthesis of VLDL.[23]

Cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) appear to promote lipid peroxidation, besides endothelial and platelet activation, and the production of reactive oxygen species.[14]

An increase in serum triglyceride concentrations is observed in HIV-infected patients as the disease progresses, particularly in the presence of opportunistic infections, possibly due to an increase in the levels of inflammatory cytokines (TNF- α, interleukins, and interferon alpha [IFN- α])[22,24] and steroid hormones.[1,18] The lower the CD4+ T lymphocyte count in peripheral blood, the higher the concentrations of triglycerides and the lower the levels of total cholesterol and LDL-c.[1,18] In contrast, low concentrations of HDL-c are found in HIV-infected patients, regardless of the CD4+ T lymphocyte count.[18,25]

HIV/AIDS, ART, and lipid alterations

Changes in lipid metabolism associated with ART use have been commonly reported in all age groups of HIV-infected patients.[5–7]

In relation to the metabolic side effects of ART, children are more vulnerable than adults because of their status as growing organisms and their longer exposure to ART.[5]

Cross-sectional studies with HIV-infected children and adolescents receiving ART have shown high frequency of dyslipidemia, lipodystrophy,[26–28] retinol, and b-carotene deficiencies[27] and, therefore, high risk for cardiovascular diseases.[28] In a multicenter study, HIV-infected children with symptoms of fat redistribution presented adiponectin

Table 1 – Studies assessing the lipid profile of patients with HIV/AIDS without ART.

Reference	Study design and treatment duration	Lipid profile alterations
Fourie et al. (2010)[19]	Sub-study from PURE HIV+ (n = 300) *versus* HIV− (n = 300): 12 years	- HIV+ *versus* HIV-: ↓HDL-c (1.23 *versus* 1.7 mmol/L); ↓LDL-c (2.6 *versus* 2.8 mmol/L); ↑TG (1.29 *versus* 1.15 mmol/L), ↑CRP (3.31 *versus* 2.13 mg/L); ↑IL-6 (4.7 *versus* 3.72 pg/L) - HIV-1 subtype C was associated with dyslipidemia
Grunfeld et al. (1991)[22]	AIDS (n = 45); HIV+ (without AIDS; n = 13); HIV− (controls; n = 17)	- AIDS: ↑IFN-α ($p < 0.001$ compared to controls); with detectable levels in 84% of AIDS patients - HIV+: three of 13 had detectable IFN-α - AIDS and HIV+: significant correlation between IFN-α and TG ($R = 0.44$, $p < 0.002$) IFN-α modulated lipid metabolism, and was probably responsible for the hypertriglyceridemia found in AIDS patients
Grunfeld et al. (1989)[1]	AIDS (n = 32); HIV+ (n = 8); HIV− (controls; n = 17)	- AIDS *versus* controls: ↑TG and prevalence of hypertriglyceridemia (50%) ($p < 0.002$ and $p < 0.005$, respectively)

ART, antiretroviral therapy; CRP, C-reactive protein; HDL-c, high density lipoprotein; IFN-α, interferon-alpha; IL, interleukin; LDL-c, low density lipoprotein; PURE, Prospective Urban and Rural Epidemiological study; TG, triglycerides.

decrease, associated with insulin resistance, increase of triglycerides and reduction of HDL-c.[29]

Pregnancy already is a condition that is characterized by important metabolic changes. The use of ART during pregnancy is associated with several concerns, which include potential teratogenicity, risk for the exposed and uninfected newborn, possible reduced efficacy of antiretroviral regimens in this particular condition, and safety considerations for the mother, including potentially increased risk of specific adverse events.[6]

HIV-infected older adults have a slower immunological response to ART and a higher risk for cardiovascular diseases, considering the factors: aging, HIV infection, and ART.[7] A multicenter cross-sectional study involving 179 elderly individuals indicated that 54% had dyslipidemia, 23% had cardiovascular diseases, and 58% had lipodystrophy.[30]

Six classes of antiretroviral drugs are currently available (Table 2).

Protease inhibitors, NRTIs, and NNRTIs are the drugs most frequently associated with lipodystrophy and alterations in lipid metabolism.[32,33] Furthermore, the drugs of each class exert distinct metabolic effects.[23]

Table 3 summarizes the results of the original studies (n = 48) that assessed the lipid profile of HIV/AIDS patients with ART.

Protease inhibitors

Elevated plasma lipid concentrations were observed in 70% to 80% of patients who received ART containing protease inhibitors. This class of antiretroviral drugs has been associated with the development of peripheral lipodystrophy, central adiposity, breast hypertrophy, and insulin resistance.[66,72–76]

Patients who use protease inhibitors for a long period of time frequently present hypertriglyceridemia, elevated concentrations of LDL-c, reduced HDL-c levels, and accumulation of apolipoprotein E and apolipoprotein CIII (apoCIII).[66,67,69,77] However, the reduction of HIV-1 viral load has been associated with an increase of serum HDL-c.[69]

In the first exploratory studies, various protease inhibitors (saquinavir, indinavir, nelfinavir, and ritonavir) were associated with different degrees of hyperlipidemia.[71,78] However, some authors found that dyslipidemic patients using protease inhibitors who switched to atazanavir-containing regimens showed improvement of lipid parameters, while the immunological and virological efficacy of the regimen was maintained.[36,42,53,79–81]

In a multicenter, prospective, observational study of 23,437 HIV-infected patients conducted by the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group (2007), an association was initially observed between the use of protease

Table 2 – Antiretroviral drugs by class.*

PI	NRTI	NNRTI	FI	CCR5 antagonist	Integrase inhibitor
Atazanavir (ATV)	Abacavir (ABC)	Efavirenz (EFV)	Enfuvirtide (T-20)	Maraviroc (MVC)	Raltegravir (RAL)
Darunavir (DRV)	Didanosine (ddI)	Etravirine (ETR)			
Fosamprenavir (FPV)	Emtricitabine (FTC)	Nevirapine (NVP)			
Indinavir (IDV)	Stavudine (d4T)				
Lopinavir (LPV)	Lamivudine (3TC)				
Nelfinavir (NFV)	Tenofovir (TDF)				
Ritonavir (RTV)	Zidovudine (AZT)				
Saquinavir (SQV)					
Tipranavir (TPV)					

PI, protease inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitors; FI, fusion inhibitor.

* Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.[31]

Table 3 – Studies assessing the lipid profile of patients with HIV/AIDS receiving ART.

Reference	Type of ART	Study design and treatment duration	Lipid profile alterations
Podzamczer et al. (2011)[34]	NVP *versus* ATZ/RTV, both combined with TDF + FTC (ARTEN Study)	Prospective study (n = 569): baseline evaluation up to 48 weeks	- NVP promoted ↑ TC, ↑HDL-c, ↑LDL-c, and ↑apoA1, but not of apoB; ATZ/r was associated with ↑ TG; NVP *versus* ATZ/r: < TC/HDL-c ratio and < apoB/apoA ratio; - Low Framingham score in the two groups
MacInnes et al. (2011)[35]	MVC *versus* EFV	Intervention study: MVC (n = 360) *versus* EFV (n = 361), both combined with AZT/3TC for 96 weeks	- For patients with TC and LDL-c below the NCEP treatment thresholds at the beginning of the study (TC: 35% × 11% in the EFV group *versus* LDL-c: 23% × 8% in the MVC group) ($p < 0.001$) - For patients exceeding the NCEP thresholds: TC: 83% × 50% ($p = 0.008$); LDL-c: 86% × 55% ($p = 0.03$); HDL-c: 43% × 62% ($p = 0.002$) (values referring to an increase for patients with HDL-c < 40 mg/dL)
Lu et al. (2011)[36]	Two NRTI +ATV 1×/day or ATV/r 1×/day	Prospective observational study (n = 66): 48 weeks	- ATV regimen was well tolerated and resulted in significant improvement of hyperlipidemia
Crane et al. (2011)[37]	Comparison between NRTI pairs used in the first ART	Cohort study (n = 2,267): patients with at least two months of ART	- TDF/3TC or TDF/FTC associated with ↓ lipid levels (TC, TG, HDL-c, LDL-c and non-HDL-c); ddI/3TC associated with ↑ LDL-c; d4T/3TC with ↑TG; ddI/d4T with ↑ HDL-c
Adewole et al. (2010)[25]	NNRTI	Cross-sectional study (n = 130): 12 months	- NNRTI containing NVP promoted ↑ HDL-c and stabilization of TC and TG
Battistini et al. (2010)[27]	ART	Cross-sectional study with children and adolescents (n = 30): median duration with ART: 28.4 months	- Lipodystrophy: 53.3% - Dyslipidemia (AIDS *versus* controls): 60% *versus* 23% ($p = 0.004$) - ↑ Frequency of dyslipidemia, lipodystrophy, and retinol and b-carotene deficiencies, but it was not possible to demonstrate a correlation of these findings with lipid peroxidation
Randell et al. (2010)[38]	TDF/3TC + FPV/RTV *versus* TDF/3TC + LPV/RTV	Intervention study (n = 27): 2×/day Pharmacokinetics was evaluated up to two weeks	- ↑ 6.6% TC with FPV and 10.9% with LPV. Similar changes in lipids and lipoprotein subfractions in the groups with ↑ TG, ↑VLDL, ↑chylomicrons and ↑LDL-c. No significant alteration in HDL-c and ↓ small-HDL-c
Palios et al. (2010)[39]	HAART *versus* untreated	Cross-sectional study (n = 40)	- Patients on HAART presented ↑ TC compared to control
Nguemaïm et al. (2010)[18]	ART	Case-control study [HIV+ (n = 172) and HIV− (n = 172)]	HIV+ *versus* HIV- subjects: - CD4 < 50 cells/μL: ↓TC and ↓LDL-c ($p < 0.0001$); ↑TG ($p < 0.001$); > TC/HDL-c ratio ($p < 0.01$); > HDL-c/LDL-c ratio ($p = 0.02$) - CD4 50–199 cells/μL: ↓TC ($p < 0.001$) and ↑TG ($p < 0.001$) - CD4 200–350 cells/μL: ↑TG ($p = 0.003$); > TC/HDL-c ($p < 0.0002$); > HDL-c/LDL-c ratio ($p = 0.04$) - CD4 >350 cells/μL: > TC/HDL-c ratio ($p < 0.0001$); > HDL-c/LDL-c ratio ($p < 0.001$) - HIV+: < HDL-c irrespective of the CD4 cell count.
Tungsiripat et al. (2010)[40]	ART with TDF	Double-blind, placebo-controlled crossover study (n = 17): 12 weeks	TDF *versus* placebo: - ↓ non-HDL-c, ↓ LDL-c and ↓TC - TDF: lipid-lowering action
Werner et al. (2010)[28]	HAART	Cross-sectional study with children and adolescents (n = 43): three months	- Lipid abnormality: 88.3%; - Body shape change: 13.9%
Bunupuradah et al. (2009)[41]	Double-boosted PI combination, SQV and LPV/r	n = 50: 12 weeks (HIV-infected children who had failed on reverse transcriptase inhibitors)	- TC and HDL-c ↑significantly over time, whereas TG and LDL-c did not -Body shape changes: Approximately 50%
Calza et al. (2009)[42]	First HAART: ABC/3TC + ATV/RTV *versus* TDF/FTC + ATV/RTV	Clinical Trial [ABC/3TC (n=42); TDF/FTC (n=47)]:48 weeks	- ABC/3TC + ATV/RTV: higher CD4 - Both groups: ↓ TG. Similar TC and LDL-c

– Table 3 (*Continued*)

Reference	Type of ART	Study design and treatment duration	Lipid profile alterations
Carosi et al. (2009)[43]	ABC/3TC + FPV/RTV (1400 mg/100 mg), 1×/day *versus* ABC/3TC + FPV/RTV (700 mg/100 mg), 2×/day	Intervention study (n = 214): follow-up for 24 and 48 weeks	- No significant alteration in non-HDL-c values in either group
Kim et al. (2009)[44]	Different HAART regimens	Single center, retrospective cohort study (n = 178). (HIV-1 infected children with HAART *versus* HIV-1 infected children without medications [controls])	- 72.4% had TC > 180 mg/dl, 53.4% had TC > 200 mg/dl - For TC > 200, the multivariable analysis showed ↑ risk with NRTI/NNRTI (HR: 1.86, 95% CI: 1.34–2.19) and NRTI/PI (HR: 3.45, 95% CI: 2.65–4.51) when compared to controls
Sarni et al. (2009)[26]	ART (80% HAART and 30% with PI)	Cross-sectional study with children and adolescents (n = 30): median duration with ART = 28.4 months	- Lipodystrophy: 53.3% - Dyslipidemia: 60% - Children on HAART with PI: > % of mixed lipodystrophy
Tao et al. (2009)[45]	Comparison of patients on HAART with and without lipodystrophy	Cross-sectional study (n = 52)	- Prevalence of hypercholesterolemia, hypertriglyceridemia, and low HDL-c levels: 17.3%, 50.0%, and 17.3%, respectively - Patients with lipodystrophy: ↑ TG and ↓ HDL-c
Mothe et al. (2009)[30]	HAART	Multicenter cross-sectional study with HIV-1-infected population aged 70 years or more (n = 179)	- Dyslipidemia: 54% -Cardiovascular disease: 23% -Lipodystrophy: 58%
Williams et al. (2009)[46]	ART	Prospective observational study (n = 433): patients received ART for a mean of eight years	- 28% hypercholesterolemia - Patients receiving RTV or NNRTI (especially EFV) presented ↑ TC and TG
Estrada and Fuster (2008)[47]	TDF+FTC+DRV/RTV *versus* TDF+FTC+LPV/RTV	Intervention study: 48 weeks (ARTEMIS)	- Similar virological and immunological response. DRV/RTV was associated with a ↓ frequency of adverse lipid effects
Calza et al. (2008)[48]	FPV/RTV *versus* LPV/RTV.	Observational study (n = 82): 18 months	- LPV/RTV: ↑ TG
Farhi et al. (2008)[49]	HAART	Cross-sectional study (n = 235)	- 77.5% prevalence of dyslipidemia
Ananworanich et al. (2008)[50]	First HAART: two NRTI + SQV/RTV	Intervention study (n = 272): 24 weeks	- ↑ TC, ↑TG, ↑LDL-c, and ↑HDL-c
Pupulin et al. (2008)[51]	HAART (68% with PI)	Cross-sectional study (n = 60): use of HAART (mean: five years)	- ↑ TC (28%), ↑ HDL-c (83%), and ↑ LDL-c (3%) suggesting an effect of HIV infection and not of HAART. 21% of patients with hypertriglyceridemia
Domingo et al. (2008)[52]	Onset of ART with two NRTI + EFZ or two NRTI + LPV/RTV	Retrospective cohort (VACH) (n = 1,550): evaluation at zero to three; three to six; six to 12; 12-18; and >18 months	- Use of LPV/RTV was associated with higher risk of early hypertriglyceridemia
Bernal et al. (2008)[21]	ART (NNRTI and PI)	Cross-sectional (n = 219): two months	- Prevalence of low HDL-c: 45%
Colafigli et al. (2008)[53]	AZT	Observational study (n = 197): follow-up for at least one month	- AZT: ↓TC, ↓HDL-c, ↓non-HDL-c, and ↓TG. Marked reduction in patients with high baseline TC and TG values. Decrease of cardiovascular risk
Kosalaraksa et al. (2008)[54]	Double boosted PI, SQV and LPV/r	n= 50: 48-weeks (children who have failed NNRTI/NRTI- based regimens)	- ↑ median TC and TG (+ 35 mg/dL; + 37 mg/dL, respectively, p < 0.001)
Tassiopoulos et al. (2008)[55]	ART	Prospective cohort study (Pediatric AIDS Clinical Trials Group 219C) (n = 2,122 perinatally HIV-infected children free of hypercholesterolemia at entry): six years	- 13% of children had hypercholesterolemia at entry - + 13% developed hypercholesterolemia during follow-up for an incidence rate of 3.4 cases per 100 person-years (95% CI: 3.0-3.9) - After adjustment for age, boosted PI use (HR: 13.9, 95% CI: 6.73-28.6), nonboosted PI use (HR: 8.65, 95% CI: 4.19-17.9), and NNRTI use (HR: 1.33, 95% CI: 1.04-1.71) were associated with ↑ risk of hypercholesterolemia, and > viral load was protective (> 50 000 *versus* ≤ 400 copies/mL; HR: 0.59, 95% CI: 0.39-0.90)

– Table 3 (*Continued*)

Reference	Type of ART	Study design and treatment duration	Lipid profile alterations
Aurpibul et al. (2007)[56]	HAART (either NVP or EFV, together with 3TC and d4T) were prospectively followed	n = 90 (Children): 144 weeks	-Central lipohypertrophy: 46%; peripheral lipoatrophy: 20%; and combined type: 34% -Hypertriglyceridemia: 12%; hypercholesterolemia: 11% -Low HDL-c decreased from 94% at *baseline* to 12% at week 144 ($p < 0.01$)
Llibre et al. (2006)[20]	Replacement of d4T with TDF	Prospective multicenter study (n = 873): 12 months	- ↓TC, ↓LDL-c and ↓TG. Patients with hyperlipidemia presented marked reduction in LDL-c and TG. The greatest reduction in TG was observed in patients with severe hypertriglyceridemia
Kumar et al. (2006)[57]	ABC+3TC+AZT *versus* AZT+3TC+NFV *versus* d4T+3TC+NFV	Intervention study: 96 weeks	- ABC+3TC+AZT: lower LDL-c - TC: ABC+3TC+AZT<AZT+3TC+NFV< d4T+3TC+NF - No change in HDL-c with any treatment
Castro-Sansores et al. (2006)[58]	HAART	Cross-sectional study (n = 211)	- 44% hyperlipidemia; 20% hypercholesterolemia; 32% hypertriglyceridemia; 14% hypertriglyceridemia + hypercholesterolemia; NRTI: more frequent lipid alterations
De Luca et al. (2006)[59]	Onset of ART: two NRTI + EFV *versus* two NRTI + LPV/r	Prospective observational cohort: 2 NRTI + EFV (n = 481); 2 NRTI + LPV/r (n = 193)	- ART regimens containing EFV or LPV with similar efficacy and tolerability - LPV was associated with higher rates of hypertriglyceridemia
Floridia et al. (2006)[6]	PI and d4T use	Observational study with HIV-infected pregnant women (n = 248)	- ↑ mean lipid values progressively and significantly during pregnancy: 141.6 mg/dL for TG ($p < 0.001$), 60.8 mg/dL for TC ($p < 0.001$), 13.7 mg/dL for HDL-c ($p < 0.001$), and 17.8 mg/dL for LDL-c ($p = 0.001$) - Women with PI *versus* without PI (at all trimesters): > mean TG - d4T: dyslipidemic effect at first trimester only
Verkauskiene et al. (2006)[29]	HIV-infected children with ART (in the majority of children, treatment was > four years)	Multicenter study (n = 130): December 2000 to April 2002	- 32 children with fat redistribution syndrome: 14 with atrophic lipodystrophy and 18 with hypertrophic lipodystrophy - ↑ TG and ↓ HDL-c in atrophic lipodystrophy *versus* no lipodystrophy - HIV-infected children with symptoms of fat redistribution: ↓adiponectin, associated with dyslipidemia
Jones et al. (2005)[60]	First HAART using different regimens: two NRTI + one NNRTI *versus* two NRTI + one PI *versus* two NRTI + two PI	Prospective longitudinal study (n = 1,664)	- d4T and PI associated with hypercholesterolemia - TDF+3TC+EFV (28 patients) without ↑TC
Keiser et al. (2005)[61]	Two NRTI + one PI changing to two NRTI + ABC *versus* maintenance two NRTI + one PI	Evaluation after 28 weeks: ABC (n = 52) or PI (n = 52)	- ABC: ↓ TC, ↓LDL-c, and ↓TG. No difference in HDL-c
Viganò et al. (2005)[62]	Patients receiving HAART containing 3TC, d4T and a PI were randomized to switch PI to EFV and d4T to TDF at baseline (Group 1) or at week 24 (Group 2)	Prospective evaluation (n = 28: 48-weeks; HIV-infected children)	- Group 1: significant ↓ in cholesterol ($p < 0.05$), ↓ HDL-c ratio ($p < 0.01$), and ↓TG ($p < 0.05$) was observed 24 and 48 weeks after the switch of HAART -Group 2: unchanged lipids in 24 weeks prior to the switch of HAART and a significant improvement on cholesterol ($p < 0.05$), HDL-c ratio ($p < 0.01$), and TG ($p < 0.05$) were observed 24 weeks after the switch of HAART
Lucas et al. (2003)[63]	HAART	Cohort study (n = 444): five years	- After four years, 35% of the patients with viral suppression developed diabetes and hyperlipidemia

– Table 3 (*Continued*)

Reference	Type of ART	Study design and treatment duration	Lipid profile alterations
Christeff et al. (2002)[64]	ART	Cross-sectional study (n = 42; 27 of whom had symptoms of lipodystrophy)	- ↑IFN-α in lipodystrophy-positive *versus* lipodystrophy-negative and controls - ↑IFN-α: positive correlation with ↑TC, ↑TG, ↑VLDL, ↑ apoB and >apoB/apoAI ratio
Galli et al. (2002)[65]	Two NRTIs	Follow-up for three months (n = 335)	- 23%: hypertriglyceridemia - 10.5%: hypercholesterolemia
Fauvel et al. (2001)[66]	PI with two NRTIs (most frequently: IDV with d4T and 3TC)	Follow-up for three months (n = 60 male)	- Carriers of the -455C variant: 30% lower levels of HDL-c than non-carriers. TG↑ according to the number of variant alleles - Apo C-III polymorphisms: genetic predisposition to develop dyslipidemia under PI therapy
Rakotoambinina et al. (2001)[67]	HAART with PI	Cohort (n = 175): 24 months	- Lipoatrophy: ↑TG - Nucleoside analog: risk factor for lipoatrophy
Thiébaut et al. (2001)[68]	HAART (PI *versus* other HAART combinations)	Prospective cohort (n = 925): 25 months	- 70 experienced hypertriglyceridemia; 4.2 cases per 100 person years (CI=3.2 ±5.2) - *Baseline* TG level and being overweight were risk factors of hypertriglyceridemia, together with advanced HIV disease. The contribution of HAART was not demonstrated
Vergis et al. (2001)[69]	ART with PI	Prospective study (n = 56): one year	- ↑TG (> 250 mg/dL): 52% - Adherence > 80% to a PI *versus* adherence < 80%: ↑LDL-c (79%); severe ↑TG (> 800 mg/dL) (21%) - < Viral load was associated with > HDL-c level
Carr et al. (1999)[70]	ART with PI *versus* ART without PI	With PI (n = 113): follow-up mean 21 months Never treated with PI (n = 45; 28 with follow-up)	- Lipodystrophy: 83% of PI recipients and 4% of treatment-naïve patients (p = 0.0001) - < Body fat: independently associated with longer duration of PI therapy and < bodyweight before therapy, and more severe lipodystrophy was associated with ↑TG and ↑C-peptide (previous [p < 0.03] and current [p ≤ 0.01], and less peripheral and greater central fat [p = 0.005 and 0.09; respectively]) - Hyperlipidemia: 74% of treated patients *versus* 28% of naïve patients (p<0.001)
Schmidt et al. (1999)[71]	PI-treated patients *versus* control group	Prospective study (n = 98)	- 57%: Hyperlipidemia - PI-treated patients *versus* control group: LDL-c=146 mg/dL (range: 53-274 mg/dL) *versus* 105 mg/dL (range: 22-188 mg/dL; p < 0.001); VLDL = .5 mg/dL (5-253 mg/dL) *versus* 18 mg/dL (range: 3-94 mg/dL; p < .001) - > Frequency of the apolipoprotein E2 allele and E4 allele: hyperlipidemic subjects - Patients with excessive hypertriglyceridemia: ↓ lipoprotein lipase activity - >Lipodystrophy: hyperlipidemic

ABC, abacavir; APV, amprenavir; ART, antiretroviral therapy; ATV, atazanavir; AZT, zidovudine; 95% CI, 95% confidence interval; DRV, darunavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; ETR, etravirine; FPV, fosamprenavir; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HR, hazard ratio; HDL-c, high density lipoprotein; IDV, indinavir;IL, interleukin; IFN-α, interferon alpha; LDL-c, low density lipoprotein; LPV, lopinavir; LPV/r, lopinavir with a booster of ritonavir; MVC, maraviroc; NCEP, National Cholesterol Education Program; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; TC, total cholesterol; TDF, tenofovir; TG, triglycerides; TNF-α, tumor necrosis factor alpha; TPV, tipranavir; 3TC, lamivudine.

inhibitors and an increased risk of myocardial infarction. However, this risk was slightly lower after adjustment for lipid concentrations.[82] In a subsequent investigation by the DAD Study Group, the best model to predict the risk of myocardial infarction derived from a dataset of 22,625 HIV-infected patients without a history of cardiovascular disease should include age, gender, systolic blood pressure, smoking status, family history of cardiovascular diseases, diagnosis of diabetes, total cholesterol, HDL-c, time of indinavir and lopinavir exposure, and current use of abacavir.[83]

The Pediatric AIDS Clinical Trials Group 219C was the first large prospective cohort study to examine the effect of protease inhibitors and other antiretroviral medications on the incidence of hypercholesterolemia among HIV-infected children and adolescents. This group indicated that the use of protease inhibitors leads to a marked increase in total cholesterol levels.[55]

Kim et al., in a retrospective cohort study involving HIV-1 infected children with highly active antiretroviral therapy (HAART) *versus* HIV-1 infected children without HAART found that those using the NRTI/protease inhibitors-regimen presented significantly higher total cholesterol levels than NRTI and NRTI/NNRTI.[44]

For children who have failed on reverse transcriptase inhibitors-based regimens, double boosted protease inhibitors, saquinavir, lopinavir, and ritonavir represents an option for second line treatment. However, the drugs significantly increased the median levels of serum cholesterol and triglycerides after 48 weeks.[54] Bunupuradah et al., in the same population, showed that, after 12 weeks, total cholesterol and HDL-c increased significantly, whereas triglycerides and LDL-c did not.[41]

In an observational study with HIV-infected pregnant women, there were differences in lipid values at each trimester by protease inhibitors and stavudine use. HIV-positive pregnant women using protease inhibitors presented a progressive increase in triglycerides and cholesterol values from the first to the third trimester.[6]

Nucleoside reverse-transcriptase inhibitors

Antiretroviral treatment regimens containing NRTIs have also been associated with alterations in body fat deposition, particularly lipoatrophy, similar to the alterations observed with protease inhibitor-containing regimens. In addition, metabolic alterations, particularly changes in serum triglyceride concentrations, are observed.[65]

However, the alterations in lipid metabolism are less evident in patients using a combination of tenofovir + lamivudine compared to those using zidovudine + lamivudine, stavudine + lamivudine, or didanosine + lamivudine, with the observation of lower serum concentrations of LDL-c, total cholesterol, and triglycerides in the former.[37,40]

The effect of regimens containing tenofovir indicates a lipid-lowering action of this NRTI and differs from that of other drugs from the same class of antiretroviral drugs.[37,40,53] Replacement of NRTIs such as stavudine with tenofovir might be a useful strategy to improve the lipid profile of patients with dyslipidemia, particularly triglyceride levels, with a consequent reduction of cardiovascular risk.[20] For HIV-infected children, switching stavudine to tenofovir is virologically and immunologically safe and provides a significant improvement in lipid profile.[62]

In contrast, the use of the NRTIs abacavir and didanosine was found to be an independent risk factor for myocardial infarction in the DAD Study.[84] Subsequently, the same group found that current use of abacavir was an independent risk factor for myocardial infarction above the measurable metabolic effects of the drug.[83]

Floridia et al. showed that stavudine was associated with dyslipidemic effect in HIV-infected pregnant women in the first trimester only.[6]

Non-nucleoside reverse-transcriptase inhibitors

ART regimens containing nevirapine are associated with a better lipid profile, mainly because they provide higher serum concentrations of HDL-c.[34,85,86] Bernal et al. observed that an undetectable viral load and NNRTI regimens containing nevirapine protected against low levels of HDL-c.[21]

The lipid profile of patients with AIDS and a previous history of severe immunodepression who achieved immune reconstitution with ART has been shown to vary according to the antiretroviral regimen used. Patients treated with protease inhibitors (booster dose of ritonavir) or efavirenz presented a significant increase of total cholesterol and triglyceride concentrations, whereas an increase of serum HDL-c levels was observed in those receiving nevirapine.[46] However, for HIV-infected children, Viganò et al. demonstrated that switching the protease inhibitor to efavirenz improved the lipid profile.[62]

Aurpibul et al. showed that, in HIV-infected children who began HAART (either nevirapine or efavirenz, together with lamivudine and stavudine), low HDL-c decreased from 94% at baseline to 12% at week 144 ($p < 0.01$); dyslipidemia occurred only in 11% to 12% of children.[56]

Possible metabolic mechanisms

Protease inhibitors are known to inhibit lipogenesis and adipocyte differentiation and to stimulate lipolysis of subcutaneous fat. NRTIs, in turn, can also reduce lipogenesis and adipocyte differentiation in subcutaneous tissue and might be one of the possible causes of mitochondrial toxicity, inhibiting mitochondrial DNA polymerase γ, which leads to the depletion of mitochondrial DNA. In addition, antiretroviral drugs have been shown to increase central visceral fat and the levels of fatty acids in blood, with a further increase of fatty acids oxidation.[23,64]

Apparently, HIV/AIDS patients receiving ART who develop lipodystrophy have higher serum concentrations of inflammatory cytokines (IL-6 and TNF-α). In addition, evidence indicates a relationship between an increase of IFN- α and elevations of serum concentrations of total cholesterol, triglycerides, VLDL, apoB, and apoB/apoA1.[64] In this respect, protease inhibitors appear to bind to LDL receptor-related protein (LRP), reducing the cleavage of fatty acids from circulating triglycerides by the LRP-lipoprotein lipase complex on vascular endothelium, and impairing the uptake of remnant hepatic chylomicrons and VLDL.[76,87] Moreover, protease inhibitors may directly stimulate hepatic triglyceride synthesis through up-regulation of

mRNA production in hepatic cells for key enzymes involved in the triglyceride biosynthetic pathway, leading to the hepatic accumulation of triglyceride-rich lipoparticles.[77]

These drugs may also modify lipoprotein metabolism by interfering with the expression of inflammatory cytokine genes and oxidative stress-related genes.[87] The expression of genes in adipocytes and hepatocytes is modulated by protease inhibitors through sterol regulatory element-binding proteins (SREBPs), cytoplasmic retinoic-acid binding protein type 1 (CRABP-1), peroxisome proliferator activated receptors (PPARs), and apoCIII, events that contribute to the development of atherogenic dyslipidemia.[3]

Carr et al. have proposed that the pathogenesis of lipodystrophy syndrome is based upon the structural similarity between the catalytic region of HIV-1 protease and CRABP-1 and LRP, probably establishing a high affinity among these elements.[76]

Protease inhibitor-induced peripheral lipodystrophy is a result of impaired CRABP1-mediated cis-9-retinoic acid stimulation of retinoid X receptor: PPAR-γ and of the capacity of protease inhibitors to inhibit cytochrome P450 3A, resulting in reduced differentiation and increased apoptosis of peripheral adipocytes. Hyperlipidemia is exacerbated by inhibition of LRP, leading to central obesity, breast fat deposition in the presence of estrogen, insulin resistance, and diabetes mellitus type 2.[76]

Bastard et al. found that protease inhibitors induce altered differentiation status of peripheral adipocytes by altering SREBP1 function *in vivo*, because this abnormal adipocyte differentiation is associated with greatly reduced SREBP1c expression. [88]

Nevertheless, the mechanisms that promote lipid alterations in HIV/AIDS patients are still not completely understood, and may be potentiated by genetic and environmental factors, as well as by medications.[23]

Conclusions

HIV-infected patients without ART presented lipid alterations associated with the infection itself, characterized by a decrease of total cholesterol, LDL-c, and HDL-c, and by an increase of triglyceride levels. In contrast, ART regimens promoted distinct alterations in the lipid metabolism of these patients. Protease inhibitors, particularly indinavir and lopinavir, were commonly associated with hypercholesterolemia, hypertriglyceridemia, elevated LDL-c, and reduced HDL-c. Fewer lipid alterations were observed with use of the protease inhibitor atazanavir. Some NRTIs (didanosine, stavudine, and zidovudine) more frequently induced lipid alterations, particularly lipoatrophy and hypertriglyceridemia. However, tenofovir-containing NRTI regimens resulted in a better metabolic profile. Patients using NNRTIs developed hypertriglyceridemia and hypercholesterolemia. The NNRTI nevirapine was particularly associated with elevated concentrations of HDL-c. Therefore, the infection itself, the different classes of drugs, and some drugs from the same class of ART appear to exert distinct alterations in lipid metabolism.

Conflict of interest

All authors declare to have no conflict of interest.

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