HIV/AIDS - Research and Palliative Care

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REVIEW

Antiretroviral Therapy-Associated Metabolic Complications: Review of the Recent Studies

This article was published in the following Dove Press journal:
HIV/AIDS - Research and Palliative Care

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Abstract: The extensive utilization of antiretroviral therapy (ART) has successfully improved human immunodeficiency virus (HIV)-associated complications. The incidence of opportunistic infections is decreased by the viral load suppression and the CD4 count promotion. However, metabolic complications, commonly bone demineralization, lipodystrophy, and lactic acidosis, are arising following the adaptation of long-term ART. The events are not drug-specific, but the severity and incidence individually vary depending upon classes of drugs. Such concerning occurrences may lead to discontinuation of current therapy or switching to another regimen with fewer adverse effects. The purpose of this review is to demonstrate the common metabolic abnormalities associated with each class of widely used ART in people living with HIV (PLHIV). Electronic databases such as PubMed, ScienceDirect, Scopus, Google Scholar, SciFinder, and Web of Science were used for the literature search. A better understanding of ART-associated metabolic adverse effects is helpful in various clinical settings so that therapists may optimize treatments in this population.

Keywords: HIV, antiretroviral therapy, lipodystrophy, metabolic, lipid profile

Introduction

Since 10 years ago, acquired immune deficiency syndrome (AIDS)-related death has declined by 39% according to the global statistics of 2020.[1] The mortality related to human immunodeficiency virus (HIV) infection has been decreased with the discovery of effective antiretroviral therapy (ART).[2,3] Globally, of the 67% of patients receiving treatment, 59% had successfully viral suppression in 2019.[1] On the other hand, the increase in survival makes HIV infection a chronic illness which requires life-long treatment. Despite therapeutic effectiveness, ART regimens have long been accompanied with various metabolic complications.[4] Consequently, ART associated metabolic abnormalities become increasing concerns among people living with HIV (PLHIV). The severity and prevalence may be varied according to the individual or the type of regimen. Highly Active Antiretroviral Therapy (HAART) are combination regimens consisting of at least three ARTs from two different mechanism of actions. Commonly used regimens are two nucleoside reverse transcriptase inhibitors (NRTIs) plus one or two protease inhibitors (PIs) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI). NRTIs such as abacavir, lamivudine, zidovudine, tenofovir, and stavudine; PIs such as lopinavir, ritonavir, saquinavir, and nelfinavir; and NNRTIs such as nevirapine, efavirenz, and etravirine have long been widely used as first or second line ART.[5]

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DovePress
http://doi.org/10.2147/HIV.S275314

Some metabolic side-effects of antiretroviral drugs include bone demineralization, increased cholesterol and triglyceride levels, and abnormalities in fat distribution.[4] Generally, the prevalence of reduced bone mineral density (BMD) was higher in PI-treated HIV-infected patients. They had three times higher prevalence of osteoporosis compared with uninfected people.[6] Lipodystrophy was a common metabolic adverse event which was associated with central adiposity, peripheral fat wasting, cushingoid feature, lipomas, and breast hypertrophy.[7] In particular, HIV-infected patients with abnormal fat distribution or lipoatrophy may experience dyslipidemia, which has become a significant issue.[8] In some HIV-infected individuals, serious metabolic events may lead to discontinuation of therapy or switching to another regimen with fewer side-effects. This review aims to better understand metabolic abnormalities associated with each class of ART, highlighting the HAART regimen. Therefore, advanced strategies for modification of therapy to mitigate complications in the HIV population can be more developed.

Methods

We performed a comprehensive literature search for the articles published between January 2000 and June 2020. Clinical trials, cross-sectional studies, and cohort studies which are available in English language were included. The articles which demonstrated metabolic abnormalities were mainly reviewed with a specific focus on lipodystrophy, abnormalities of lipid profiles, glucose levels, and bone. Other interesting side-effects related to ART were also thoroughly reviewed. Exclusion criteria were pilot studies, research protocols, conference proceedings, book chapters, review papers, and articles without full text. Terms such as human immunodeficiency virus/HIV/antiretroviral therapy/acquired immunodeficiency syndrome/metabolic/lipodystrophy/lipoatrophy/lactic acidosis/bone demineralization/osteopenia/dyslipidemia/nucleoside reverse transcriptase inhibitor/abacavir/zidovudine/lamivudine/stavudine/tenofovir disoproxil fumarate (tenofovir DF)/tenofovir alafenamide (tenofovir AF)/didanosine/emtricitabine/non-nucleoside reverse transcriptase inhibitor/nevirapine/efavirenz/etravirine/rilpivirine/protease inhibitor/lopinavir/ritonavir/atazanavir/darunavir/indinavir/nelfinavir/saquinavir/integrase inhibitor/dolutegravir/raltegravir were used to search in the electronic databases: PubMed, ScienceDirect, Scopus, Google Scholar, SciFinder, and Web of Science.

Pathophysiology

Lipodystrophy refers to the abnormal distribution of adipose tissue.[9] It includes lipohypertrophy, which is fat accumulation in central areas: abdomen, breast, neck, and lipoatrophy, which is loss of fat in proximal areas: face, arms, legs, buttock. The exact etiology of lipodystrophy is still unknown.[9] The issue that should be emphasized is both ART and HIV cause changes in lipid distribution. The production of inflammatory cytokines such as interleukins are provoked, which results in adipose cell destruction. Moreover, insulin signaling function and glucose transport were impaired. As a consequence, ART associated lipodystrophy increases the risk for dyslipidemia, insulin resistance, diabetes mellitus, and heart disease.[10] Dyslipidemia is the condition in which total cholesterol levels above 5 mmol/L, triglycerides >1.7 mmol/L, and low-density lipoprotein cholesterol (LDL-C) levels of >3 mmol/L.[11] Lactic acidosis is also common, which referred to the level of uncuffed lactate >5 mmol/L and arterial pH <7.35 or a total venous carbon dioxide <20 mmol/L.[11] In some patients receiving ART, there was elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (>40 U/L) which were predictive factors of metabolic complications also in the general population.[12]

Animal Studies

The safety and efficacy of antiretroviral drugs have been monitored, as has the metabolic alteration during the treatment period tested in preclinical trial studies.[13–16] Conradie et al[13] examined the effects of ART on bone metabolism and lipodystrophy in rats. Stavudine (6.2 mg/kg), tenofovir DF (26.6 mg/kg), lopinavir/ritonavir (70.8 mg/kg), and water (1.5 mL) were subjected orally to 40 male rats for 9 weeks. Under examination by dual energy X-ray absorptiometry (DEXA), stavudine monotherapy was associated with a decrease in femoral BMD (0.247 ± 0.02 g/cm^2, $P<0.05$). Biomechanical testing showed that the load-bearing capacity and strength of femurs of stavudine-treated rats were significantly lower than those of other groups ($P<0.05$). Both NRTIs (stavudine and tenofovir) resulted in significant bone marrow adiposity. Another NRTI, zidovudine, also reduced BMD in mice.[14] Mice were orally treated with 0.25 mg zidovudine daily for 4 weeks while controls received water. Under examination by DEXA, zidovudine treated mice showed a significant decrease in BMD ($P<0.04$). Metabolic consequences of PIs administration in mice

has been reported.[15,16] C57BL/6 mice were assigned combined lopinavir/ritonavir (50/12.5 to 200/50 mg/kg) for 3 weeks. There were significant changes in metabolic parameters showing hyperlipidemia, hyperinsulinemia, and lipodystrophy symptoms as the dose-dependent manner. The findings indicated that PIs, particularly lopinavir/ritonavir treatment, result in lipodystrophy symptoms which are similar to those found in human.[15] Tsai et al[16] examined the 4-week treatment effects of lopinavir/ritonavir in C57BL/6 mice. Increased total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels were observed in addition to intracellular lipid accumulation. In a mice model, daily administration of abacavir/lamivudine and lopinavir/ritonavir may probably increase metabolic disorders regardless of HIV infection.[16]

In vitro Studies

Lipin-1 is a gene necessary for the normal development of adipose tissues.[17] HIV-infected patients with lipodystrophy or metabolic abnormalities due to ART have decreased lipin-1 mRNA expression in subcutaneous adipose tissues.[18] In differentiated 3T3-L1 cells, treatments with PIs resulted in reduction in lipin-1 mRNA expression by promoting the miRNA-218 expression. Although the role of miRNA is still ambiguous, it was reported to have a relationship with glucose transporter type 4 (GLUT-4) gene expression which is the insulin-stimulated glucose transporter. During treatment with PIs, increased miRNA caused reduction in GLUT-4 which in turn resulted in insulin resistance and metabolic abnormalities. 3T3-L1 adipocytes on exposure to lopinavir: ritonavir combination showed a significant reduction in lipid (−13.2% in concentration of 12 μM:3 μM and −14.5% in 16 μM:4 μM, $P<0.05$).[18] Caron et al[19] examined the long-term effects of NRTIs on lipid accumulation and mitochondrial function of differentiating 3T3-F442A and differentiated 3T3 adipocytes. Among the treated NRTIs, zidovudine (1 μM) and stavudine (10 μM) showed changes in lipid phenotype, content, and expression of metabolic markers. Thus, in vitro after 6–11 days of zidovudine and stavudine treatment at near C_{max} concentrations, there were decreases in lipid content, survival of adipose cells, and mitochondrial activity. These results seemed to be relevant to the lipodystrophy of patients treated with low dose concentrations for months or years of treatment period. Nolan et al[20] explored the effect of cellular mitochondrial DNA (mtDNA) reduction in patients receiving NRTIs therapy. The amount of mtDNA was significantly decreased in NRTIs (zidovudine/stavudine) group compared to ART-naïve HIV-positive controls ($P<0.001$). There were also abnormalities of adipose tissue among patients receiving NRTIs.

Genetic and Ethnic Influence

The risk of metabolic abnormalities including dyslipidemia can be predicted by genetic factors. The effects of apolipoprotein C3 (APOC3), apolipoprotein E (APOE) on ART-associated lipid abnormalities have been explored.[21] The effects of alleles of APOC3 and APOE on plasma cholesterol and triglycerides in patients receiving ritonavir were prospectively monitored over 3-year study period. Triglyceride levels were significantly high in patients who had alleles of APOC3-482CT, −455TC, and −3238CG ($P=0.006$). Meanwhile, there were elevations of non-high density lipoprotein cholesterol (non-HDL-C) levels in patients with APOE-3/4 and E-4/4 genotypes ($P=0.038$). Similarly, Fauvel et al[22] evaluated the influence of APOC3 gene polymorphism on dyslipidemia in male patients receiving PIs. Indinavir, ritonavir, saquinavir, and nelfinavir were administered in combination with two NRTIs; stavudine and lamivudine. During a 3-month period, plasma triglycerides were elevated, and HDL-C levels were decreased in those patients ($P<0.01$).

The prevalence of metabolic complications was varied among different ethnic groups. Curtis et al[23] highlighted the prevalence of metabolic bone abnormalities in a cohort of PLHIV under HAART. Non-African-Americans had higher risk of osteopenia (59%) than African-Americans (26%). Mean urinary N-telopeptide levels were also higher in non-African-Americans. Glucose levels were also varied among ethnicities. HIV-infected African-Americans and Hispanics had higher risk of diabetes than non-Hispanic whites.[24] HbA1c and 2 hour glucose levels were significantly higher in African-Americans than Hispanics or non-Hispanic whites. Ethnicity was also related to CD4 counts in patients on HAART which affect insulin sensitivity. In the occurrence of lipodystrophy due to NRTIs therapy, the increased risk was provoked in White patients ($P=0.023$).[25] This finding also suggested that there are differences in severity of metabolic variation among PLHIV based on ethnicity. In patients on PI regimens, the risk of dyslipidemia can be predicted by ethnicity.[26] African-Americans and Hispanics had higher levels of triglycerides than White HIV-infected patients on exposure to non-ritonavir PI regimens. However, on exposure to ritonavir regimens, all groups tended to increase in triglycerides.

Metabolic Complications Associated with ART in HIV-Infected Patients

The metabolic outcomes in HIV-infected patients receiving different classes of antiretroviral drugs in previous publications are summarized in Table 1. Questionnaires, abnormalities reports, physical measurements, and clinical assessments including evaluations of laboratory parameters such as CD4, HIV-1 RNA, lipid profiles, glucose, and serum lactate were applied in these studies.

NRTI-Associated Metabolic Complications

Several studies have reported the lipodystrophy occurrence in NRTI-treated HIV-infected patients.[11,28–32] Zidovudine and stavudine can cause lipodystrophy with different incidence.[28] Patients in the stavudine arm had more frequent symptoms of peripheral fat depletion compared to those in the zidovudine therapy. The fat depletion was presented by atrophy on the face, lower limb, buttock, and venomegaly (P=0.011, 0.006, 0.009, and 0.001, respectively). There were elevations in cholesterol, triglyceride, and glucose levels but they were not significantly different between the two groups. Univariate analysis showed that older patients and female genders had increased risk of central fat accumulation. Consistently, Menezes et al[11] reported the metabolic toxicity of stavudine during a median follow-up of 19 months in their prospective cohort study. The prevalence of abnormalities was 17.1% peripheral neuropathy, 5.7% symptomatic hyperlactatemia, 2.5% lactic acidosis, and 7.3% lipoatrophy in the study group on stavudine. They examined that patients with a body mass index (BMI) of 25–30 kg/m^2 or >30 kg/m^2 had higher risks of hyperlactatemia and lactic acidosis. Moreover, females had higher metabolic toxicities such as diabetes and dyslipidemia. The findings concur with the previous study.[28] In contrast, male gender was associated with lipodystrophy in the study by Alikhani et al.[29] The prevalence of lipodystrophy in this study was 47%, with a mean trunk/limb fat ratio of 1.87. Patients with lipodystrophy were at risk of development of diabetes and dyslipidemia following the elevations of blood glucose and triglyceride levels (P=0.002 and P<0.001, respectively). Additional factors such as duration of HIV infection, year of exposure to zidovudine or stavudine, and older age were also associated with lipodystrophy.

In a clinical trial of Gallant et al,[30] where the safety and efficacy of tenofovir DF versus stavudine in ART-naïve patients were assessed, the overall incidence of laboratory abnormalities were similar. Lower mean elevations in triglycerides (+0.01 mmol/L), total cholesterol levels (+0.78 mmol/L), LDL-C levels (+0.36 mmol/L), and higher increase in HDL-C levels (+0.23 mmol/L) were found in the tenofovir DF group. All the patients with lactic acidosis were from the stavudine group. In addition, patients with abnormal AST and ALT levels were more frequent in the stavudine group. Tenofovir DF receiving patients had higher loss of limb fat compared to the stavudine arm at week 96 (7.9 kg vs 5 kg), and at week 144 (8.6 kg vs 4.5 kg) (P<0.001). Surprisingly, the proportions of bone fractures showed no difference between two groups, whereas researcher-reported lipodystrophy was more common in stavudine receiving patients (P<0.001). This finding was supported by the study of Haubrich et al.[31] They reported that lipoatrophy was most frequent with stavudine-containing regimens. Median cholesterol levels were also elevated in the stavudine group (41 mg/dL, P=0.02). Regimens containing didanosine/stavudine were associated with greater limb fat loss.[33] In an open-label randomized study by Gallant et al,[32] limb fat mass measured by DEXA showed that patients receiving tenofovir DF/emtricitabine had higher limb fat loss compared to the zidovudine/lamivudine group (P=0.03). The fasting lipid profile showed that the zidovudine/lamivudine group had a greater mean increase in total cholesterol (0.91 mmol/L vs 0.54 mmol/L, P<0.001) and LDL-C (0.52 mmol/L vs 0.34 mmol/L, P=0.01) compared to the tenofovir DF/emtricitabine group. Patients in the zidovudine/lamivudine group experienced more frequent adverse events which resulted in discontinuation of treatment. The study found that the most frequent cause of discontinuation of zidovudine/lamivudine containing regimen was anemia.

Sax et al[35] examined treatment-naïve patients who were randomly assigned to oral tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine in combination with either 10 mg tenofovir AF or 300 mg tenofovir DF. This study reported that the tenofovir DF group had significantly greater decreases in BMD at hip (mean % change −2.95 vs −0.66, P<0.0001) and at spine (−2.86 vs−1.3, P<0.001) compared to the tenofovir AF group at week 48. A decrease in BMD induced by tenofovir DF at week 48 was supported by the clinical trial of Chen et al.[36]

NNRTI-Associated Metabolic Complications

The use of NNRTIs showed alterations in metabolic parameters although the changes were not as much pronounced

Table 1 The Clinical Studies Reported Metabolic Effects of Antiretroviral Therapy[7,11,27–35,37,39–49,51,52]

No	Author, Year	Study Design	Methods	Participants (n)	ART Regimens	Metabolic Outcomes
1	Clumeck et al, 2001	Multicenter, randomized, double-blind open-label clinical trial	-Clinical examinations (adverse event reports, hematology tests: CD4, HIV-1 RNA, lipid profiles)	ABC group – 105 PI group – 106	ABC+2NRTIs vs PI+2NRTIs	-Change in TG (−0.14 mmol/L vs +0.04 mmol/L)[b] -Lipodystrophy in PI group (n=5)
2	Joly et al, 2002	Cross-sectional study	-Clinical examinations (body shape changes, hematology tests: CD4, HIV-1 RNA, lipid profiles, fasting glucose)	d4T group – 47 AZT group – 54	d4T+3TC+IDV vs AZT+3TC+IDV	Peripheral fat depletion, -Facial atrophy (48% vs 22%) -Lower limb atrophy (49% vs 22%) -Buttock atrophy (47% vs 20%) -Venomegaly (57% vs 24%)
3	Walmsley et al, 2002	Multicenter, randomized, double-blind clinical trial	-Clinical examinations (adverse event report, hematology tests: CD4, HIV-1 RNA, lipid profiles)	LPV/r (NFV placebo) group – 326 NFV (LPV/r placebo) group – 327	LPV/r+3TC+d4T vs NFV+3TC+d4T	-Diarrhea (15.6% vs 17.1%) -Increased AST/ALT (4.5% vs 5.2%) -Hypercholesterolemia (9% vs 4.9%) -Hypertriglyceridemia (9.3% vs 1.3%)
4	Martínez et al, 2003	Multicenter, randomized, open-label clinical trial	-Clinical examinations (Clinical data, hematology tests: CD4, HIV-1 RNA, glucose, lipid profiles)	NVP group – 155 EFV group – 156 ABC group – 149	NVP+2NRTIs vs EFV+2NRTIs vs ABC+2NRTIs	No. of patients at risk at 12 months, -Hypertriglyceridemia (107 vs 100 vs 99) -Hypercholesterolemia (108 vs 102 vs 100)
5	Gallant et al, 2004	Multicenter, randomized, double-blind clinical trial	-DEXA (whole body) -Clinical examinations (adverse event report, weight, hematology tests: CD4, HIV-1 RNA, lactate, urine, creatinine, lipid profiles)	TDF group – 299 d4T group – 301	TDF+3TC+EFV vs d4T+3TC+EFV	-Lipodystrophy (3% vs 19%) At week 144, -Total limb fat loss (8.6 kg vs 4.5 kg)[a] -Lumbar spine BMD loss (2.2% vs 1%) -Hip BMD loss (2.8% vs 2.4%) -TG (+1 mg/dL vs +134 mg/dL)[a] -TC (+30 mg/dL vs +58 mg/dL)[a] -LDL-C (+14 mg/dL vs +26 mg/dL)[a]
6	Dube et al, 2005	Multicenter, randomized, open-label clinical trial	-DEXA (whole body) -Clinical examinations (Hematology tests: CD4, HIV-1 RNA, glucose, insulin, lipid profiles)	NFV group – 99 EFV group – 110 NFV+EFV group – 125	NFV vs EFV (ddI+d4T or AZT+3TC)	-Limb fat changes (−13.1% vs +1.8%)

(*Continued*)

Table 1 (Continued).

No	Author, Year	Study Design	Methods	Participants (n)	ART Regimens	Metabolic Outcomes
7	Gallant et al, 2006	Multicenter, randomized, open-label clinical trial	-DEXA (whole body) -Clinical examinations (hematology tests: CD4, HIV-1 RNA, lipid profiles)	TDF+FTC+EFV – 258 AZT+3TC+EFV – 259	TDF+FTC+EFV vs AZT+3TC+EFV (NVP in case of serious side effects of EFV)	-Anemia (1 vs 13 patients) -Limb fat loss (19.6 lb vs 15.2 lb)[a] -TC (+21 mg/dL vs +35 mg/dL)[a] -LDL-C (+13 mg/dL vs +20 mg/dL)[a]
8	Shlay et al, 2007	Randomized, clinical trial	-Anthropometric assessments (skinfold, circumference) -BIA -Clinical examinations (clinical data, hematology tests: CD4, HIV-1 RNA, glucose, insulin, lipid profiles)	PI group – 141 NNRTI group – 141 PI+ NNRTI group – 140	PI (NFV, IDV, IDV/r, LPV/r) vs NNRTI (EFV, NVP, DLV) vs PI+ NNRTI	-Change in TG (15.15 mg/dL vs 24.87 mg/dL vs 34.99mg/dL)[a] -Change in TC (16.94 mg/dL vs 21.64 mg/dL vs 28.93 mg/dL)[a] -Change in LDL-C (8.46 mg/dL vs 7.85 mg/dL vs 12.84 mg/dL)[a] -Change in glucose (3.27 mg/dL vs 4.88 mg/dL vs 5.21 mg/dL)[a] -Change in insulin (3.86 μlu/mL vs 2.95 μlu/mL vs 2.69 μlu/mL)[a]
9	Lazzarin et al, 2007	Randomized, double-blind, placebo-controlled, phase III trial	-Clinical examinations (adverse event report, hematology tests: CD4, HIV-1 RNA, lipid profiles)	ETV group – 295 Placebo group – 296	ETV group vs Placebo group	Grade 3 or 4 abnormalities: -Increased TG (7% vs 4%) -Increased LDL-C (7% vs 7%) -Increased TC (5% vs 4%) -Increased AST (3% vs 1%) -Increased ALT (2% vs 1%) -Hyperglycemia (3% vs 2%)
10	Tebas et al, 2007	Metabolic sub-study of a randomized controlled trial	-DEXA (whole, regional body composition) -Clinical examinations (hematology tests: lipid profiles, glucose, insulin, lactate)	NRTI-sparing group – 31 PI-sparing group – 31	LPV/r +EFV vs 2NRTIs+EFV (2NRTIs= AZT+3TC (or) d4T +3TC (or) ddI+3TC (or) ddI +d4T)	At week 48, -Limb fat (+562 g vs −242 g)[b] -TG (+85 mg/dL vs +11 mg/dL)[b] -TC (+19 mg/dL vs −7 mg/dL)[b] At week 102, -Limb fat (+782 g vs −850 g)[b]
11	Madruga et al, 2007	Multicenter, randomized, phase III, open-label clinical trial	-Anthropometric assessments -Clinical examinations (hematology tests: AST, ALT, lipid profiles)	DRV/r group – 298 LPV/r group – 297	DRV/r vs LPV/r	-Increased ALT (both 9%) -Increased AST (7% vs 9%) -Increased TG (19% vs 25%) -Increased TC (32% vs 29%) -Increased LDL-C (19% vs 17%)

12	Ortiz et al, 2008	Multicenter, randomized, phase III, open-label clinical trial	-Anthropometric assessments -Clinical examinations (vital sign, electrograph, hematology tests: CD4, HIV-1 RNA, lipid profiles, glucose)	DRV/r group – 343 LPV/r group – 346	DRV/r+ TDF+FTC vs LPV/r+ TDF+FTC	-Increased ALT (8% vs 10%) -Increased AST (both 9%) -Hyperbilirubinemia (<1% vs 3%) -Increased TG (3% vs 11%) -Increased TC (13% vs 23%) -Increased LDL-C (13% vs 10%) -Hyperglycemia (6% vs 7%)
13	Duvivier et al, 2009	Multicenter, randomized, open-label clinical trial	-DEXA -Clinical examinations (clinical data, hematology tests: CD4, HIV-1 RNA, lipid profiles)	PI+NNRTI group – 36 PI+NRTI group – 19 NNRTI+NRTI group – 16	-PI+NNRTI -PI+NRTIs -NNRTI+NRTIs	-Decreased BMD at lumbar spine (−4.4 vs −5.8 vs −1.5) % -Decreased BMD at hip (−2.3 vs −3.7 vs −2.7) %
14	Haubrich et al, 2009	Multicenter, randomized, phase III, open-label clinical trial	-DEXA (whole body) -Clinical examinations (adverse event report, hematology test: CD4, HIV-1 RNA, lipid profiles)	753	-EFV -LPV -EFV-LPV -TDF -AZT -d4T	At week 96, lipoatrophy -32% -17% -9% -9% -27% -42%, respectively
15	Martin et al, 2009	Randomized, open-label clinical trial	-DEXA (bone and soft tissue) -Clinical examinations (clinical data, hematology tests: CD4, HIV-1 RNA, lipid profiles)	TDF/FTC group – 178 ABC/3TC group – 179	TDF+FTC vs ABC+3TC	-Spine BMD T-score (−0.04 vs 0.07)[a] -Right hip BMD T-score (−0.07 vs 0.09)[a]
16	Lennox et al, 2009	Multicenter, randomized, double-blind clinical trial	-Clinical examinations (adverse event reports, hematology tests: HIV-1 RNA, CD4, lipid profiles)	RAL-group – 281 EFV- group – 282	RAL+TDF+FTC vs EFV+TDF+FTC	-Change in TC (0.55 mmol/L vs 1.82 mmol/L)[a] -Change in LDL-C (0.33 mmol/L vs 0.89 mmol/L)[a] -Change in TG (−0.16 mmol/L vs 2.08 mmol/L)[a]
17	Molina et al, 2010	Multicenter, randomized, open-label clinical trial	-Clinical examinations (adverse event report hematology tests: CD4, HIV-1 RNA, lipid profiles)	ATZ/r group – 440 LPV/r group – 443	ATZ/r+ TDF/FTC vs LPV/r+ TDF/FTC	-Hyperbilirubinemia (44% vs <1%) -ALT elevation (3% vs 2%) -AST elevation (3% vs 1%) -Hypercholesterolemia (11% vs 25%) -Hypertriglyceridemia (<1% vs 4%) -Gastrointestinal adverse events

(*Continued*)

Table 1 (Continued).

No	Author, Year	Study Design	Methods	Participants (n)	ART Regimens	Metabolic Outcomes
18	Menezes et al, 2011	Prospective cohort study	-Clinical examinations (Chest X-ray, clinical data, hematology tests: CD4, HIV-1 RNA, lactic acid, lipid profiles)	d4T-based therapy – 8497 Other drug – based therapy – 543	d4T vs Other ART	-Peripheral neuropathy (17.1% vs 11.2%) -Symptomatic hyperlactatemia (5.75% vs 2.2%) -Lactic acidosis (2.5% vs 1.3%) -Lipoatrophy (7.3% vs 4.6%)
19	Fätkenheuer et al, 2012	Randomized, double-blind, placebo-controlled clinical trial	-Clinical examinations (adverse event report, hematology tests: CD4, HIV-1 RNA, lipid profiles)	ETV group – 79 EFV group – 78	ETV+2NRTIs vs EFV+2NRTIs	-Increased TC (from 4.3 to 4.7 mmol/L vs from 4.2 to 5.2 mmol/L)[a] -Increased LDL-C (from 2.6 to 2.8 mmol/L vs from 2.4 to 3 mmol/L)[a] Grade 3 or 4 elevations: -TC >7.8 mmol/L (1% vs 8%) -LDL-C >4.9 mmol/L (3% vs 10%) -TG >8.5 mmol/L (0% vs 3%)
20	Arathoon et al, 2013	Randomized, phase III, open-label clinical trial	-Anthropometric measurements -Clinical examinations (adverse event reports, hematology tests: CD4, HIV-1 RNA, lipid profiles, glucose)	Patients on DRV/r – 343 Patients on LPV/r – 346	DRV/r 800/100 mg vs LPV/r 800/200 mg (+ fixed-dose TDF 300 mg/FTC 200 mg)	-Metabolic and nutrition disorders (14% vs 22 %) -Lipid-related adverse effects (8% vs 16%) (hypertriglyceridemia, hypercholesterolemia, hyperlipidemia, increased LDL-C)
21	Sax et al, 2015	Two randomized, double-blind, phase III clinical trials	-DEXA -Clinical examinations (adverse event reports, hematology tests: CD4, HIV-1 RNA, lipid profiles)	TAF group – 866 TDF group – 867	TAF (+EVG+C+FTC) vs TDF (+EVG+C+FTC)	At week 48, -Change in hip BMD (−0.66% vs −2.95) -Change in spine BMD (−1.3% vs −2.86)
22	Dirajlal-Fargo et al, 2016	Randomized, open-label clinical trial	-CT -DEXA -Clinical examinations (weight, hematology tests: CD4, HIV-1 RNA, fasting glucose, insulin, hs-CRP)	ATZ group – 109 RAL group – 106 DRV group – 113	ATZ/r+ TDF+ FTC RAL+ TDF+ FTC DRV/r+ TDF+ FTC	At week 96, -Change in glucose (3 mg/dL vs 6 mg/dL vs 2 mg/dL)[b] -Change in HOMA-IR (2.02 vs 2 vs 1.88)[b]
23	Perez-Molina et al, 2016	Multicenter, randomized, open-label clinical trial	-DEXA -Anthropometric assessments -Clinical examinations (adverse event reports, neurological tests, hematology tests: CD4, HIV-1 RNA, vitamin D, lipid profiles)	ATZ/r+3TC (dual therapy) – 133 ATZ/r+2NRTIs (triple therapy) – 134	Dual therapy vs Triple therapy	At week 96, -Hyperbilirubinemia (65% vs 65.9%) -Change in TG (12.1% vs −6.2%) -Change in TC (5.1% vs −1.9%) -Lumber BMD T-score (−10.3% vs −4.6%)

24	Mills et al, 2016	Multicenter, randomized, open-label, phase III controlled clinical trial	-DEXA (hip and spine) -Clinical examinations (clinical data, hematology tests: CD4, HIV-1 RNA, lipid profiles)	TAF group – 959 TDF group – 477	TAF vs TDF	At week 48, -Hip BMD T-score (0.11 vs −0.02) -Spine BMD T-score (0.17 vs −0.02) -Osteopenia (6% vs 5%) -TC (202 vs 183 mg/dL) -TG (131 vs 112 mg/dL) -LDL-C (125 vs 114 mg/dL)
25	Alikhani et al, 2019	Cross-sectional study	-DEXA (body fat) -Clinical examinations (clinical data, hematology tests: CD4, HIV-1 RNA, fasting lipid profiles, glucose,)	166	AZT d4T RAL	Lipodystrophy

Notes: [a]Mean; [b]Median.

Abbreviations: ABC, abacavir; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TC, total cholesterol; TG, triglyceride; d4T, stavudine; AZT, atazanavir; 3TC, lamivudine; IDV, indinavir; LPV, lopinavir; r, ritonavir; NFV, nelfinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NVP, nevirapine; EFV, efavirenz; DEXA, dual energy X-ray absorptiometry; TDF, tenofovir disoproxil fumarate; BMD, bone mineral density; LDL-C, low-density lipoprotein cholesterol; ddI, didanosine; FTC, emtricitabine; BIA, bioelectrical impedance analysis; NNRTI, non-nucleoside reverse transcriptase inhibitor; ETV, etravirine; DRV, darunavir; RAL, raltegravir; ATZ, atazanavir; TAF, tenofovir alafenamide; EVG, elvitegravir; C, cobicistat; CT, computed tomography; HOMA-IR, homeostatic model assessment of insulin resistance.

as other classes of drugs.[8] In contrast to other classes, NNRTIs cause only a modest increase in lipid profiles. Martínez et al[37] conducted a multicenter, randomized, open-label clinical trial in 15 centers in Spain. The efficacy of NNRTIs (nevirapine or efavirenz) or abacavir as a substitute for a protease inhibitor in HIV-infected patients was studied at baseline, 1-month, 3-month, and every 3-month period until 12-month follow-up. The proportion of patients with elevated triglycerides (>4.5 mmol/L) and cholesterol values (>6.2 mmol/L) was higher in the NNRTI group. The median fasting plasma glucose levels were also significantly higher in patients receiving efavirenz at every follow-up time (P<0.01). The efficacy and safety analysis of a randomized trial found that efavirenz had higher grade 2–4 lipid disorders than rilpivirine.[38] During the week 96 treatment period, efavirenz had higher elevations of LDL, AST, and ALT levels than rilpivirine. Lazzarin et al[39] performed a randomized, double-blind, placebo-controlled, Phase III trial in HIV-infected patients who failed by ART with resistance to NNRTIs and PIs. The patients were randomly assigned to receive either etravirine 200 mg or placebo, twice daily in combination with darunavir/ritonavir, NRTIs, and optional enfuvirtide. During a 24-week study period, grade 3 or 4 changes in laboratory lipid parameters (hyperglycemia, hypercholesterolemia, hypertriglyceridemia, increased AST and ALT) were observed which were generally similar between treatment arms. Fewer lipid elevations in etravirine were reported in a trial study by Fätkenheuer et al.[40] Of the 157 ART-naïve patients, 79 patients were assigned to etravirine 400 mg once daily with efavirenz placebo, and 78 patients were assigned to efavirenz 600 mg once daily with etravirine placebo, plus two NRTIs in both regimens. NRTIs included in this study were abacavir/lamivudine, zidovudine/lamivudine, or tenofovir/emtricitabine. At week 48, the efavirenz group showed significant elevations of lipids compared with the etravirine group: total cholesterol (+0.61 mmol/L, P<0.0001), HDL-C (+0.15 mmol/L, P=0.004), LDL-C (+0.35 mmol/L, P=0.005), and triglycerides (+0.33 mmol/L, P=0.03). Patients receiving abacavir/lamivudine in both groups showed a high increase in total cholesterol levels compared to those taking tenofovir/emtricitabine (P=0.005). The etravirine group showed fewer grade 3 elevations of lipids than the efavirenz group. The study suggested larger, long-term trials for the assessment of safety and efficacy of etravirine 400 mg once daily. In addition to an increase in lipid parameters, NNRTIs such as nevirapine, efavirenz, and

delavirdine also increased insulin resistance.[41] There was a significant elevation of mean insulin levels over the median study period of 5 years ($P<0.01$). This supported the close monitoring of risk of diabetes and glucose levels. Moreover, efavirenz in combination with NRTI (tenofovir DF) has been examined to reduce BMD in HIV-infected ART-naïve patients.[36]

PI-Associated Metabolic Complications

The use of PIs was associated with a significant increase in lipid levels leading to hyperlipidemia. The lipid abnormalities due to PIs are severe and more common than other classes of drugs,[8] some of which resulted in discontinuation of the treatment.[42] In a clinical trial of Clumeck et al,[43] patients receiving PI-based therapy for at least 6 months were examined. The only recommended PI during randomization was ritonavir/saquinavir. Increased lipid profiles (triglyceride >2.3 mmol/L and cholesterol >5.2 mmol/L) were found in these patients. Some patients discontinued treatment because of lipodystrophy and significant elevation in triglyceride and cholesterol levels. Similarly, abnormally higher triglycerides and total cholesterol levels due to PIs were also observed in a study of Walmsley et al.[7] Patients on lopinavir/ritonavir regimens had higher abnormalities in laboratory profiles than those on nelfinavir regimens. During the 48-week period, the mean elevations in total cholesterol were 1.37 mmol/L vs 1.24 mmol/L, and in triglycerides were 1.4 mmol/L vs 0.5 mmol/L in these groups. Lipodystrophy or lipoatrophy were reported but the prevalence was not much pronounced. The study suggested a longer follow-up time over 48 weeks to determine the clinical significance of elevations in lipids. When compared to efavirenz (NNRTI), nelfinavir was found with greater loss of limb fat in a randomized study by Dube et al[33] ($P<0.003$). Lipid profile measurements also showed high elevations in the nelfinavir group over 64 weeks.

Ortiz et al[44] randomly subjected ART-naïve patients to receive either darunavir/ritonavir or lopinavir/ritonavir, in combination with tenofovir/emtricitabine. Grade 2–4 elevations in triglycerides and cholesterol were found more frequently in the lopinavir group than the darunavir group (11% vs 3%, and 23% vs 13%, respectively) at week 48. This finding was supported by the week 48 phase III trial of Madruga et al.[45] The grade 2–4 elevations of AST and ALT were also observed in addition to the same incidence of hyperglycemia in two groups. Hypertriglyceridemia and hypercholesterolemia were the adverse events leading to permanent treatment discontinuation found in the lopinavir/ritonavir group. In a randomized trial of Molina et al,[46] ART-naïve patients were subjected to receive atazanavir/ritonavir or lopinavir/ritonavir, each in combination with tenofovir/emtricitabine. Bilirubin-associated adverse events were higher in the atazanavir group. Some changes in lipid parameters (increased AST, ALT, cholesterol, and triglycerides) were significantly higher in the lopinavir group ($P<0.0001$) at week 96. Additionally, the patients in the lopinavir group had higher gastrointestinal intolerability rates, in which 1.6% of patients discontinued the treatment due to diarrhea. This study recommended atazanavir/ritonavir as the first-line treatment because it has a better lipid profile and high efficiency in treatment-naïve patients with high plasma HIV viral loads and low CD4 counts at baseline.

Arathoon et al[42] conducted a 192-week, randomized, Phase III, open-label trial to compare the efficacy and safety of darunavir/ritonavir and lopinavir/ritonavir, each in combination with fixed-dose tenofovir/emtricitabine in ART-naïve patients. Metabolic-related adverse effects were observed at week 96. Two patients on lopinavir-based regimens discontinued treatment due to hypercholesterolemia and hypertriglyceridemia. The occurrence of metabolic and nutritional disorders was higher in the lopinavir group. The most frequent lipid-related adverse events were hypertriglyceridemia (2% vs 5.8%), hypercholesterolemia (1.5% vs 4%), hyperlipidemia (0.6% vs 3.2%), and increased LDL-C (2.3% vs 1.2%) in the darunavir and lopinavir groups. Some anthropometric changes such as body weight or mid-waist/hip ratio were observed in week 96, but these were considered clinically irrelevant. PI containing regimens increased insulin resistance prevalence and glucose level in HIV-infected patients in previous randomized studies.[41,47] AIDS Clinical Trials Group (ACTG) A5260s, a trial study, examined the changes in insulin resistance after treatment with raltegravir, darunavir/ritonavir, or atazanavir/ritonavir in ART-naïve HIV-infected patients.[47] At the follow-up period of week 96, there were increases in homeostatic model assessment of insulin resistance (HOMA-IR) in all study groups. It was also observed that such an increase in insulin resistance was associated with changes in BMI, interleukin-6, and high-sensitivity C-reactive protein at week 48 and 96. Bone abnormalities were also pronounced in patients receiving PIs. In a randomized study of ART-naïve patients, BMD changes were monitored at baseline and week 48 by DEXA.[48] The randomized regimens were PIs plus NNRTI and PIs plus NRTI or NNRTI plus NRTIs.

At week 48, there were significant decreases in BMD at lumbar spine and hip (mean −4.1 and −2.8, $P \leq 0.001$, respectively). BMD at lumbar spine was decreased more prominently in PI receiving patients compared to regimens without PIs.

Other ART-Associated Metabolic Complications

Lipodystrophy was associated with the cumulative use of antiretroviral drugs such as raltegravir.[29] Patients with fat abnormalities were more likely to develop diabetes and dyslipidemia. However, raltegravir showed better safety and clinical profiles in a trial reported by Lennox et al.[49] ART-naïve patients were randomized to receive either 400 mg raltegravir twice daily or 600 mg efavirenz once daily, both in combination with tenofovir and emtricitabine. Fasting LDL-C >4.92 mmol/L and triglycerides >3.48 mmol/L were found more frequently in the efavirenz group. Mean LDL-C and triglyceride levels were higher in the efavirenz than the raltegravir group after week 48.

Switching Strategies

Several studies have recommended to switch or simplify the regimens in order to reverse the treatment-related abnormalities such as metabolic disorders, fat redistribution, or other manageable side-effects.[30,34,37,43,50–53] Clumeck et al[43] demonstrated that switching from a PI-based regimen (ritonavir/saquinavir) to abacavir-based regimen provides prolonged viral suppression and significant improvements in lipid abnormalities. Switching from a stable PI regimen to atazanavir/ritonavir was found to improve insulin resistance and dyslipidemia in HIV-infected men.[54] After 3 months, there were increases in glucose disposal rate (P=0.008), and a significant decrease in triglyceride levels also (P=0.023). Carr et al[53] observed that switching from nucleoside analogs such as zidovudine or stavudine to abacavir resulted in improvement in HIV-associated lipoatrophy. There was a significant increase in limb fat mass on DEXA in abacavir receiving patients (0.39 kg) compared to the zidovudine or stavudine arm (0.08 kg), 95% CI= 0.06–0.57, P=0.02. Nonetheless, a larger study population and longer follow-up period were recommended to decide whether lipoatrophy can be improved clinically or resolved. ACTG 5125s studied the effects of PIs and NRTIs on the fat distribution, BMD, and metabolic parameters in patients with advance HIV (CD4 ≤200 cells/mm^3 or viral load ≥80,000 copies/mL) and undetectable viral load.[51] Patients were randomized to switch their initial regimen to open label lopinavir/ritonavir plus efavirenz or two NRTIs plus efavirenz. During a median observation period of 102 weeks, the PIs group had a greater increase in limb fat, meanwhile the NRTIs arm had loss of limb fat. However, at week 48, the PIs group had greater increases in triglycerides (85 vs 11 mg/dL, P=0.01), total cholesterol (19 vs −7 mg/dL, P=0.009),

Table 2 Antiretroviral Therapy Associated with Lipodystrophy[7,11,28–33,37,43]

Name of Drug	Reference
Nucleoside reverse transcriptase inhibitors	
Abacavir	Martínez et al, 2003
Emtricitabine	Gallant et al, 2006
Lamivudine	Gallant et al, 2006
Stavudine	Joly et al, 2002 Gallant et al, 2004 Haubrich et al, 2009 Menezes et al, 2011 Alikhani et al, 2019
Tenofovir disoproxil fumarate	Gallant et al, 2004 Gallant et al, 2006 Haubrich et al, 2009
Zidovudine	Joly et al, 2002 Gallant et al, 2006 Haubrich et al, 2009 Alikhani et al, 2019
Non-nucleoside reverse transcriptase inhibitors	
Efavirenz	Martínez et al, 2003 Haubrich et al, 2009
Nevirapine	Martínez et al, 2003
Protease inhibitors	
Lopinavir	Walmsley et al, 2002 Haubrich et al, 2009
Nelfinavir	Walmsley et al, 2002 Dube et al, 2005
Saquinavir	Clumeck et al, 2001
Ritonavir	Clumeck et al, 2001 Walmsley et al, 2002
Integrase inhibitor	
Raltegravir	Alikhani et al, 2019

Table 3 Summary of the Effects of Antiretroviral Therapy on Metabolic Parameters[7,11,27,29,30,32–35,37,39,40,42–46,49,51,52]

Name of Drug	TC	TG	LDL-C	HDL-C	BMD	Glucose	Lactate	References
Nucleoside reverse transcriptase inhibitors								
Abacavir	↑		↑	↑	↑		↑	Martin et al, 2009
Didanosine	↑			↑				Dube et al, 2005
Lamivudine	↑	↑	↑	↑	↑			Gallant et al, 2006 Martin et al, 2009
Emtricitabine	↑	↑	↑	↑				Gallant et al, 2006
Stavudine	↑	↑	↑	↑	↓	↑	↑	Gallant et al, 2004 Dube et al, 2005 Menezes et al, 2011 Alikhani et al, 2019
Tenofovir AF	↑	↑	↑		↓			Sax et al, 2015 Mills et al, 2016
Tenofovir DF	↑	↑	↑	↑	↓			Gallant et al, 2004 Gallant et al, 2006 Martin et al, 2009 Sax et al, 2015
Zidovudine	↑	↑	↑	↑				Gallant et al, 2006 Alikhani et al, 2019
Non-nucleoside reverse transcriptase inhibitors								
Efavirenz	↑	↑	↑	↑		↑		Martínez et al, 2003 Dube et al, 2005 Lennox et al, 2009 Fätkenheuer et al, 2012
Etravirine	↑	↑						Lazzarin et al, 2007
Nevirapine	↑	↑				↑		Martínez et al, 2003
Protease inhibitors								
Atazanavir	↑	↑						Molina et al, 2010 Perez-Molina et al, 2016
Darunavir	↑	↑	↑	↓		↑		Arathoon et al, 2012
Lopinavir	↑	↑		↑, ↓		↑		Walmsley et al, 2002 Tebas et al, 2007 Madruga et al, 2007 Ortiz et al, 2008 Molina et al, 2010
Nelfinavir	↑	↑						Walmsley et al, 2002 Dube et al, 2005
Ritonavir	↑	↑		↑				Clumeck et al, 2001 Walmsley et al, 2002 Tebas et al, 2007 Madruga et al, 2007 Ortiz et al, 2008 Molina et al, 2010
Saquinavir	↑	↑						Clumeck et al, 2001

(*Continued*)

Table 3 (Continued).

Name of Drug	TC	TG	LDL-C	HDL-C	BMD	Glucose	Lactate	References
Integrase inhibitors								
Raltegravir	↑	↑	↑			↑		Lennox et al, 2009 Alikhani et al, 2019

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMD, bone mineral density.

and non HDL-C (13 vs −10 mg/dL) compared to NRTIs group. It was also found that, at week 48, treatment changes in body mass were directly related to changes in fasting insulin concentration. On the other hand, changes in total cholesterol and triglyceride levels were inversely related to baseline BMI and lean mass. After a median follow-up of 2.1 years, the PIs group showed a higher treatment discontinuation rate than the NRTIs group (40 vs 19, $P<0.001$, respectively). This rate was mainly forced by increased triglyceride levels. Although the lopinavir/ritonavir arm improved limb fat mass, their significant increase in lipid parameters suggested careful therapeutic management.

Martin et al[34] conducted a randomized, open-label, 96-week trial in HIV-infected patients by switching from the existing NRTIs to either tenofovir/emtricitabine or abacavir/lamivudine. The baseline NRTIs included abacavir without tenofovir, tenofovir without abacavir, lamivudine, emtricitabine, zidovudine, didanosine, and stavudine. In the overall 357 patients, the abacavir group had more common lipid-related events compared to the tenofovir group ($P=0.003$). However, bone events such as osteopenia or osteoporosis were more common in the tenofovir group ($P=0.032$). In addition, the tenofovir regimen was not only associated with rapid decreases in body weight and lean body mass but also led to significant loss of hip and spine BMD. In a trial of Perez-Molina et al,[52] ART-experienced patients were randomized into either dual therapy with atazanavir/ritonavir plus lamivudine or triple therapy with atazanavir/ritonavir plus two NRTIs (tenofovir/emtricitabine or abacavir/lamivudine or zidovudine/lamivudine). From baseline to 96 weeks, analysis showed that two patients per group discontinued ART because of hyperbilirubinemia but there was no new discontinuation beyond 48-week duration. Increased total cholesterol and triglyceride levels were observed in the dual therapy arm. A decrease in BMD was also observed but there were no significant different changes between groups. Mills et al[27] conducted a multicenter, randomized, open-label, phase III clinical trial in treatment experienced HIV-infected adults. Participants were randomly assigned at a 2:1 ratio into either switching into single tablet tenofovir AF (n=959) 10 mg plus elvitegravir 150 mg, cobicistat 150 mg and emtricitabine 200 mg or continuing previous tenofovir DF regimens (n=477). At week 48, mean BMD at the hip and spine remained stable or decreased in the tenofovir DF group, whereas there were increases in the tenofovir AF group ($P<0.0001$). Patients on previous tenofovir DF regimens tended to improve BMD after switching to tenofovir AF regimens. Consistent with this finding, Maggiolo et al[55] observed the significant improvement in BMD after switching from tenofovir DF to tenofovir AF containing regimens in HIV-infected patients aged 60 years or older.

According to previous studies, PLHIV receiving to ART exhibited the changes in subcutaneous adipose tissues, commonly lipodystrophy and abnormal lipid profiles. Lists of antiretroviral drugs in each class associated with lipodystrophy are summarized in Table 2. Although lipodystrophy in patients receiving abacavir, nevirapine, or efavirenz had been decreased, newer cases were arising. Therefore, switching from PIs to these drugs in order to reduce tendency for discontinuation due to lipid abnormalities is still not an applicable strategy.[37] Individual drugs with their effects on changes in metabolic markers are summarized in Table 3. Types of ART with different metabolic profiles can be differentiated. Although some known drugs do not have optimal safety and tolerability profiles, their side-effects do not limit the efficacy in clinical settings. NRTIs (abacavir, lamivudine, zidovudine, emtricitabine, tenofovir), NNRTIs (nevirapine, efavirenz), and PIs (lopinavir, ritonavir, atazanavir) are commonly recommended in the first-line HAART regimens.[5] Each antiretroviral drug with their common metabolic complications examined in previous studies are summarized in Table 4.

Recommendations

The prevalence or severity of metabolic abnormalities are varied among individuals or classes of drugs; some of

Table 4 The Common Metabolic Effects of Antiretroviral Therapy[7,11,27–35,37–40,42–46,48–53,56]

Drug	Effects	References
Nucleoside reverse transcriptase inhibitors		
Abacavir	Lipodystrophy Hypertriglyceridemia Hypercholesterolemia Lactic acidosis	Clumeck et al, 2001 Carr et al, 2002 Martínez et al, 2003 Fätkenheuer et al, 2012
Zidovudine	Leukopenia Anemia Lipodystrophy Peripheral neuropathy Hypercholesterolemia Hypertriglyceridemia Facial atrophy Lower limb atrophy Buttock atrophy Lactic acidosis	Carr et al, 2002 Joly et al, 2002 Gallant et al, 2006 Tebas et al, 2007 Haubrich et al, 2009 Fätkenheuer et al, 2012 Tetteh et al, 2016 Alikhani et al, 2019
Lamivudine	Lipodystrophy Anemia Peripheral neuropathy Hypercholesterolemia Hypertriglyceridemia Decreased BMD at lumbar spine Decreased BMD at hip Facial atrophy Lower limb atrophy Buttock atrophy Hyperbilirubinemia	Joly et al, 2002 Walmsley et al, 2002 Gallant et al, 2004 Tebas et al, 2007 Fätkenheuer et al, 2012 Perez-Molina et al, 2016 Tetteh et al, 2016 Alikhani et al, 2019
Stavudine	Peripheral neuropathy Hyperlactatemia Lipoatrophy Anemia Hypercholesterolemia Hypertriglyceridemia Decreased BMD at lumbar spine Decreased BMD at hip Facial atrophy Lower limb atrophy Buttock atrophy Lactic acidosis	Carr et al, 2002 Joly et al, 2002 Walmsley et al, 2002 Gallant et al, 2004 Dube et al, 2005 Gallant et al, 2006 Tebas et al, 2007 Haubrich et al, 2009 Menezes et al, 2011 Tetteh et al, 2016
Tenofovir disoproxil fumarate	Lipoatrophy Anemia Hypercholesterolemia Hypertriglyceridemia Decreased BMD at lumbar spine Decreased BMD at hip Osteopenia	Gallant et al, 2004 Gallant et al, 2006 Haubrich et al, 2009 Lennox et al, 2009 Martin et al, 2009 Sax et al, 2015 Mills et al, 2016
Tenofovir alafenamide	Decreased BMD at lumbar spine Decreased BMD at hip Osteopenia	Sax et al, 2015 Mills et al, 2016
Didanosine	Lipoatrophy Limb fat loss	Dube et al, 2005 Tebas et al, 2007
Emtricitabine	Anemia Hypercholesterolemia Hypertriglyceridemia Lipoatrophy Decreased BMD at lumbar spine Decreased BMD at hip	Gallant et al, 2006 Martin et al, 2009 Lennox et al, 2009 Fätkenheuer et al, 2012
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine	Anemia Peripheral neuropathy Hypertriglyceridemia Hypercholesterolemia Decreased BMD at lumbar spine Decreased BMD at hip	Martínez et al, 2003 Duvivier et al, 2009 Tetteh et al, 2016
Efavirenz	Anemia Peripheral neuropathy Hypertriglyceridemia Hypercholesterolemia Increased AST, ALT Lipoatrophy Decreased BMD at lumbar spine Decreased BMD at hip	Martínez et al, 2003 Gallant et al, 2004 Duvivier et al, 2009 Gallant et al, 2006 Haubrich et al, 2009 Lennox et al, 2009 Cohen et al, 2013 Fätkenheuer et al, 2012 Tetteh et al, 2016
Etravirine	Hypercholesterolemia Hypertriglyceridemia Increased AST	Lazzarin et al, 2007 Fätkenheuer et al, 2012
Rilpivirine	Hypercholesterolemia Increased AST, ALT	Cohen et al, 2013
Protease inhibitors		
Lopinavir	Lipid abnormalities Metabolic and nutritional disorders Lipoatrophy Hypercholesterolemia Hypertriglyceridemia Gastrointestinal disorders Increased AST, ALT Decreased BMD at lumbar spine Decreased BMD at hip Hyperbilirubinemia Hyperglycemia	Walmsley et al, 2002 Madruga et al, 2007 Tebas et al, 2007 Ortiz et al, 2008 Duvivier et al, 2009 Haubrich et al, 2009 Molina et al, 2010 Arathoon et al, 2013
Ritonavir	Lipid abnormalities Metabolic and nutritional disorders Decreased BMD at lumbar spine Decreased BMD at hip Hypercholesterolemia Hypertriglyceridemia Hyperbilirubinemia Hyperglycemia	Clumeck et al, 2001 Madruga et al, 2007 Ortiz et al, 2008 Duvivier et al, 2009 Arathoon et al, 2013

(*Continued*)

Table 4 (Continued).

Drug	Effects	References
Atazanavir	Hyperbilirubinemia Hypercholesterolemia Hypertriglyceridemia Gastrointestinal disorders Decreased BMD at lumbar spine Increased AST, ALT	Molina et al, 2010 Perez-Molina et al, 2016
Darunavir	Lipid abnormalities Metabolic and nutritional disorders Hypercholesterolemia Hypertriglyceridemia Increased AST/ALT Hyperbilirubinemia Hyperglycemia	Madruga et al, 2007 Ortiz et al, 2008 Arathoon et al, 2013
Indinavir	Decreased BMD at lumbar spine Decreased BMD at hip Facial atrophy Lower limb atrophy Buttock atrophy	Joly et al, 2002 Duvivier et al, 2009
Nelfinavir	Hypercholesterolemia Hypertriglyceridemia Increased AST, ALT Limb fat loss	Walmsley et al, 2002 Dube et al, 2005
Saquinavir	Lipodystrophy Hypertriglyceridemia	Clumeck et al, 2001
Integrase inhibitors		
Dolutegravir	Lipid abnormalities Gastrointestinal disorders	Elzi et al, 2017
Raltegravir	Lipodystrophy Gastrointestinal disorders Hypercholesterolemia	Lennox et al, 2009 Elzi et al, 2017 Alikhani et al, 2019

Abbreviations: BMD, bone mineral density; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

which may be developed over time. Therefore, a longer study period is required to better recognize long-term abnormalities related to different classes of drugs. One more point to be noted is that the nutritional status of HIV-infected patients is affected by several metabolic complications due to both HIV infection and ART. Therefore, it is required to manage ART-associated metabolic abnormalities because HIV-infected patients require life-long therapy. Otherwise, patients with poor nutritional status will be exacerbated. Lifestyle management and pharmaceutical interventions are necessary for patients on long-term therapy. Nutritional counseling and intervention may be required especially in the patients who are at risk of malnutrition. In advance, dietary consideration should be provided to optimize treatment associated complications such as dyslipidemia, glucose abnormalities, and limb fat loss.[57] Individualization is also critical in relation to the treatment of metabolic abnormalities in combination with giving interventions according to each patient's needs.

Conclusion

Some drugs with high metabolic toxicity are still being used in resource-limited countries due to cost effectiveness. Thus, appropriate pharmacologic development and protocols are necessary to minimize toxicity. Nutritional counseling and management in PLHIV have been strongly recommended. The occurrence of ART-associated metabolic complication may be applied as predicting factors for either modification of therapy in PLHIV or finding new regimens with fewer side-effects. Active pharmacovigilance programs are recommended in HIV care programs to properly identify ART-related adverse events so that serious complications can be improved.[56] Moreover, strategies which differentiate PLHIV at high risk of metabolic complications may be helpful in exploring the appropriate regimens. At the beginning of ART in PLHIV, it has been highly recommended to perform genotyping.[21] Genetic polymorphism and ethnicities in some way may be related to the effects of ART. The better choice of ART regimen based on genetic analysis may help reducing the potential risk of metabolic abnormalities. Because of the multifactorial nature of metabolic complications, it is advisable to adjust the benefits and risks, including virologic success and potential toxicities of new regimens when switching or adding to the existing regimens. Prospective studies evolving the safety and efficacy of individual antiretroviral therapy or combination regimens in a large population are warranted. To get a sustained clinical benefit of therapy, pharmacologic improvements in administration of regimens have been recommended. The particular adverse effects of each drug or regimen should be clarified to achieve the effectiveness of therapy and improve the tolerability of treatment in HIV-infected patients.

Acknowledgment

This review was supported by Thailand International Cooperation Agency Scholarship.

Disclosure

The authors report no conflicts of interest in this work.

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