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HIV Protease Inhibitors and Obesity

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Abstract

Purpose of review—To review the current scientific literature and recent clinical trials on HIV protease inhibitors (PIs) and their potential role in the pathogenesis of lipodystrophy and metabolic disorders.

Recent findings—HIV PI treatment may affect the normal stimulatory effect of insulin on glucose and fat storage. Further, chronic inflammation from HIV infection and PI treatment trigger cellular homeostatic stress responses with adverse effects on intermediary metabolism. The physiologic outcome is such that total adipocyte storage capacity is decreased, and the remaining adipocytes resist further fat storage. This process leads to a pathologic cycle of lipodystrophy and lipotoxicity, a pro-atherogenic lipid profile, and a clinical phenotype of increased central body fat distribution similar to the metabolic syndrome.

Summary—PIs are a key component of antiretroviral therapy and have dramatically improved the life expectancy of HIV-infected individuals. However, they are also associated with abnormalities in glucose/lipid metabolism and body fat distribution. Further studies are needed to better define the pathogenesis of PI-associated metabolic and body fat changes and their potential treatment.

Keywords

HIV; protease inhibitors; metabolic disorders; lipodystrophy

Introduction

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) were first recognized in 1981 by the US Centers for Disease Control and Prevention[1]. Since then, the impact of AIDS and/or HIV on demographic, social, and economic conditions has been substantial. According to the World Health Organization, ~60 million people have been infected with HIV and 25 million people worldwide have died of the disease. In 2008, ~33.4 million people were living with HIV/AIDS and ~2.7 million people were newly infected2. HIV/AIDS has thus become a leading cause of mortality

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worldwide and ranks as one of most important infectious diseases facing civilization in the 21st century. There are two distinct serotypes of human AIDS viruses, HIV type 1 (HIV-1) and type 2 (HIV-2), with HIV-1 accounting for the majority of infection worldwide[3]. The majority of untreated individuals with HIV infection develop AIDS within 7–10 years.

Although Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for ~67% of HIV infections worldwide, some countries in Eastern Europe (such as Ukraine and the Russian Federation) are experiencing severe and growing national epidemics. In the United States (US), although the incidence of HIV infection has remained relatively stable, new epidemiological patterns have evolved; for instance, rates of new HIV infection in women, minorities, and younger gay men have increased, while the rate of new HIV infection among injecting drug users has fallen.

Treatment of HIV infection: HAART

The successful introduction in 1995 of highly active antiretroviral therapy (HAART), a combination of potent antiretroviral agents, has substantially decreased mortality among HIV-infected patients4, 5. HAART is the standard of care to avoid selection of viral mutations, and the regimen is typically chosen based on the patient's comorbidities, efficacy and tolerability in clinical trials, potential drug interactions, adverse drug effects, and potential long-term complications6. Furthermore, selection of drugs for treatment-naïve and treatment-experienced patients take into account the benefit/risk ratio and the HIV genotype. Current US and international guidelines recommend that treatment-naïve patients receive a combination of two nucleoside reverse-transcriptase inhibitors (NRTI) together with one non-nucleoside reverse-transcriptase inhibitors (NNRTI) or one (ritonavir-boosted) protease inhibitor (PI), and that treatment-experienced patients receive a combination of at least two active ART drugs from different classes based on the viral genotype6–8. Treatment of experienced patients that have failed previous regimens is more complex and might include newer ritonavir-boosted PIs such as darunavir or tipranavir, the new NNRTI etravirine, the CCR5 inhibitor maraviroc or the integrase inhibitor raltegravir. Currently, there are 25 antiretroviral drugs available in six different classes approved for clinical use in the treatment of AIDS9*. New drugs are also constantly in development10, 11*. Over the past two decades the treatment of HIV has advanced considerably, changing HIV from a deadly infection into a manageable complex infection requiring lifelong treatment[12–14].

However, HAART is associated with a number of metabolic and anthropometric abnormalities, including dyslipidemia and insulin resistance as well as subcutaneous fat loss (lipoatrophy) and abdominal obesity (lipohypertrophy), all of which may contribute to an increased risk of cardiovascular disease (CVD)[15]. Furthermore, besides the side effects from HIV treatment, there is recognition that HIV infection by itself, or in combination with genetic and/or environmental factors, may cause metabolic abnormalities due to the dynamic relationship between the virus and the host. In view of this, it is noteworthy that increased mortality and morbidity rates from CVD has been reported among HIV-infected patients16. As the HIV-positive population ages, the combination of cardiovascular risk factors commonly seen in the general population with the presence of HIV infection and its treatment thus pose significant therapeutic and health care challenges.

Protease Inhibitors

PIs were first introduced in 1996 and have resulted in dramatic decline in HIV-related mortality and morbidity; thus, they remain a cornerstone of antiretroviral therapy. Nine PIs are currently available: saquinavir, indinavir, ritonavir, nelfinavir, lopinavir, fosamprenavir, atazanavir, darunavir and tipranavir (Table 1).

However, soon after their introduction, safety concerns for lipodystrophy[19] and associated metabolic complications such as insulin resistance[20] and dyslipidemia[21] were raised, and although several studies have established an association between the use of PI therapy and a wide range of adverse effects, the clinical significance of these findings remains unknown[22–24]. Results from cross-sectional studies have shown that compared to healthy subjects, HIV-positive patients receiving antiretroviral therapy have increased secretion and decreased clearance of VLDL particles[25], increased synthesis[26] and reduced catabolism of apolipoprotein B[27], the protein backbone of atherogenic lipoproteins, and diminished lipoprotein lipase activity[28]. Hypertriglyceridemia and increased levels of pro-atherogenic remnant lipoproteins have also been noted in HIV-positive patients on HAART[21, 29]. Furthermore, until recently, a high pill burden for many PIs caused poor adherence. This problem has in part been solved by newer PIs, which have more convenient formulations with fewer pills and once-daily administration.

PIs prevent cleavage of viral polyproteins after viral budding and thereby inhibit the ability of virus particles to infect new host cells30, [31]; they have no effect on cells already harboring integrated proviral DNA. Most PIs are only moderately absorbed in the gastrointestinal (GI) tract and absorption is increased when PIs are taken with food, except fosamprenavir, for which the fasting state is recommended. PIs distribute into most body compartments, and diffusion through anatomical barriers is usually moderate, with only indinavir penetrating the blood-brain and blood-testis barriers in therapeutic concentrations[32, 33]. Plasma protein binding is primarily to α_1-acid glycoprotein and albumin, and all the PIs, except indinavir, are highly protein-bound (Table 1). PIs are primarily metabolized through the cytochrome P450 (CYP) system in the liver (major) and small intestine (minor)[34–36]. Furthermore, beyond being substrates for CYP isozymes, the PIs are also inhibitors of CYP3A4, causing variable elimination half-lives for the drugs, ranging from 1–2 hours for saquinavir to 10–15 hours for darunavir (Table 1). As the most potent CYP3A4 inhibitor, ritonavir inhibits CYP450-mediated metabolism in the small intestine and liver, and ritonavir-boosted PIs show increased plasma minimum concentrations (Cmin), maximum concentrations (Cmax), and plasma half-lives ($t_{1/2}$). Thus, lower doses of ritonavir are used in combination with other PIs, except for nelfinavir, which is metabolized by CYP 2C19. Table 1 shows the list of all available PIs and current treatment guidelines for drug-naïve individuals. Hepatic metabolism is the primary route of biotransformation for PIs, which may therefore potentiate drug-drug interactions with this class of agents as well[17]. During last 3–4 years, many clinical trials among treatment-naïve populations such as KLEAN[37], CASTLE[38] and ARTEMIS[39] have expanded the ritonavir-boosted PI treatment options (Table 2). Furthermore, two third generation PI agents – tipranavir and darunavir – have been approved and are important therapeutic options for treatment-experienced patients (Table 1).

In general, PIs show an acceptable safety profile. The most common acute adverse effects are GI intolerance, such as nausea, vomiting, diarrhea, and bloating, which vary in intensity among different PIs. Recurrent or chronic diarrhea is the most common adverse effect, but it rarely occurs with indinavir, atazanavir, or fosamprenavir47. The incidence of diarrhea is 15–20% in patients treated with lopinavir/ritonavir48. Newer PIs, such as atazanavir/ritonavir (evaluated in the CASTLE study38) and darunavir/ritonavir (evaluated in the pooled data analysis of the POWER 1 and POWER 2 trials44) have shown a reduced incidence of such events. The PI-associated dyslipidemic pattern described above has most commonly been reported among patients receiving old PIs, such as indinavir, nelfinavir, and ritonavir49. The newer PI atazanavir is specifically less likely to induce lipid abnormalities compared with other PIs50. For example, atazanavir/ritonavir demonstrated a better lipid profile than lopinavir/ritonavir in a 96-week study51. Nephrolithiasis is also a unique adverse effect of indinavir, occurring in as many as 12.4% of patients52. Furthermore, both

atazanavir and indinavir are associated with isolated indirect hyperbilirubinemia (Gilbert's syndrome)[53]. Other morphological abnormalities (lipodystrophy - fat atrophy and fat deposition) and metabolic disturbances (hyperglycaemia and hyperlipidemia) are outlined below.

PI-Associated Body Fat Abnormalities

Changes in body fat distribution – often referred to as HIV/HAART-associated lipodystrophy – are common in HIV-infected individuals and typically start to occur after 6–12 months of PI therapy. Importantly, these body fat changes include both lipoatrophy and lipohypertrophy[19, 22, 54]. Lipoatrophy denotes a decrease in adipose tissue volume, and is an HIV-specific change that occurs with HIV/HAART therapy affecting all subcutaneous adipose tissue depots55; the least amount of subcutaneous fat loss occurs in the upper trunk, contributing to the characteristic “buffalo hump” in HIV-treated patients[55]. Alternatively, lipohypertrophy denotes an increase in adipose tissue volume, and most commonly occurs in visceral adipose tissue (VAT) and adipose tissue depots in the upper trunk, particularly in the breast and dorsocervical fat pads[55]. Lipohypertrophy, particularly of VAT, may occur concomitantly with lipoatrophy of subcutaneous fat depots56–58, suggesting that the two processes are not linked and differentially regulated. Moreover, the HIV drug factors that play a role in lipoatrophy do not appear to contribute to lipohypertrophy; rather, lipohypertrophy is associated with effective viral suppression, restored health, and weight gain[56–58].

This abnormal HIV/HAART-associated redistribution of fat has important clinical implications. First, the physical manifestations of lipodystrophy (i.e., the “buffalo hump” and truncal obesity with facial/limb wasting) may affect adherence to an otherwise successful HAART regimen in a body-image conscious individual, resulting in poor self-esteem, immunological and clinical deterioration, and non-adherence with treatment regimens that could lead to potential viral mutations and drug resistance[59, 60]. Second, increased VAT, even in the absence of HIV infection, is associated with systemic inflammation, which may negatively affect not only a patient's response to HAART, but also accelerate their lifetime risk of CVD and other adverse events15, 61, 62. Third, and of profound metabolic importance, the circulation of free fatty acids (FFAs) and triglycerides (TGs) in the bloodstream during the fat redistribution process may increase the possibility of “ectopic” fat deposition (i.e., the deposition of fat in non-adipose tissues such as the liver, skeletal muscle, heart, and pancreas).

The evaluation of ectopic lipid deposition in organ dysfunction is an area of active investigation, and the literature on this topic has recently been reviewed[63, 64**]. To summarize the major findings: *(i)* ectopic intracellular lipid deposition in the skeletal muscle (intramyocellular lipid [IMCL]) is associated with insulin resistance and inflammatory processes[65, 66]; *(ii)* ectopic intracellular lipid deposition in the liver (intrahepatocellular lipid [IHCL]) is associated with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), insulin resistance, and inflammatory processes[67, 68**]; *(iii)* ectopic lipid deposition in the heart (myocardial lipid) is associated with cardiovascular dysfunction and heart failure[69, 70]; and *(iv)* ectopic lipid deposition in the pancreas (pancreatic lipid) is associated with beta-cell dysfunction and altered insulin secretion[71, 72*]. Fat redistribution during HIV/HAART may also promote insulin resistance through altered secretion of adipokines (including adiponectin, leptin, plasminogen activator inhibitor-1 [PAI-1], resistin, tumor necrosis factor-alpha [TNF-α], and other inflammatory markers including interleukins 6 [IL-6], 8 [IL-8], and 10 [IL-10], and macrophage chemotactic protein-1 [MCP-1]), which act as both paracrine factors in adipose tissue and endocrine factors affecting both systemic glucose and lipid metabolism73. Overweight HIV

patients with increased VAT treated with PIs are at particularly high risk for disordered glucose metabolism74. Moreover, the expansion of VAT that occurs during HIV/HAART therapy is associated with macrophage infiltration, decreased adiponectin secretion, and the release of inflammatory factors73, 75, all of which are associated with insulin resistance and its associated metabolic traits.

The etiology of HIV/HAART-associated lipodystrophy is most likely multifactorial in nature (Figure 1). HIV infection itself causes dysregulation of cytokines (such as TNF-α, IL-1, and IL-6) that affect both lipid/glucose metabolism and insulin sensitivity23, and the HIV-1 virus encodes several proteins (such as Vpr and Tat) that change the activity of the glucocorticoid receptor in target tissues (such as fat and liver), causing glucocorticoid hypersensitivity and insulin resistance76, 77. In addition, the secretion of inflammatory cytokines – either in response to HIV infection and/or HAART – increase expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), thus increasing the intracellular conversion of inactive cortisone to active cortisol; in adipose tissue, this would cause increased lipolysis and release of FFAs which could then be deposited in ectopic tissues78. PIs in particular also have many other effects connecting them to altered metabolism and the pathogenesis of lipodystrophy. First, as noted above, PIs inhibit degradation of apolipoprotein B and affect the secretion of apolipoprotein B-containing lipoprotein particles from the liver79. Second, PIs inhibit insulin signaling pathways by reducing insulin-induced phosphorylation of insulin-receptor substrate (IRS) 1 and protein kinase B (PKB, also termed Akt)80. Third, PIs affect cellular levels of peroxisome proliferator-activating receptor (PPAR) γ and CCAAT/enhancer-binding protein (C/EBP) α, both of which are important in preadipocyte differentiation into mature adipocytes, as well as sterol regulatory element binding protein 1 (SREB-1), which regulates gene expression of enzymes involved in cholesterol, fatty acid, and glucose metabolism81, 82. Fourth, PIs suppress the function of the glucose transporter GLUT-4, diminishing insulin-stimulated glucose uptake83. Fifth, PIs stimulate the production of reactive oxygen species84, which can damage important intracellular organelles; mitochondrial dysfunction may then promote fatty infiltration in liver and muscle, further exacerbating insulin resistance[85].

In addition to adults, children also experience HIV/HAART-associated metabolic complications and lipodystrophy[60, 86], particularly when exposed to PI therapy[87]. The abnormalities in fat distribution can be especially distressing to a child, leading to low self-esteem and embarrassment[87]. Furthermore, PIs increase the risk of developing diabetes with age[88], putting children on PI therapy at especially high risk. Thus, given that the development of these HIV/HAART-associated conditions in children may have long-lasting social and health implications, further study of the side effects of PI therapy in the pediatric population is warranted.

Management strategies for the morphologic changes associated with HIV/HAART-induced lipodystrophy have been recently reviewed[89, 90]. Both pioglitazone91 and pravastatin92have shown some promise for the treatment of lipoatrophy; however, to date, no pharmacological agent has been shown to definitely improve HIV/HAART-associated lipoatrophic changes. Alternatively, interventions that have been shown to be efficacious for HIV/HAART-associated lipohypertrophy include metformin93, 94, recombinant human growth hormone (rGH)95*, 96, tesamorelin (a growth hormone-releasing factor)97, 98, and diet and exercise99–102. Reconstructive surgical interventions to correct the physical abnormalities associated with HIV/HAART-associated lipodystrophy have also been studied[103, 104], and may be a reasonable option in appropriate surgical candidates; however, their long-term efficacy have not been established. Given that the clinical and laboratory data suggest that the underlying biological mechanisms of lipoatrophy and lipohypertrophy differ, no single

agent/intervention is likely to manage all aspects of HIV/HAART-associated lipodystrophy. Rather, each entity should be considered and treated separately.

Conclusions

PIs are a key component of antiretroviral therapy and have dramatically improved the life expectancy of HIV-infected individuals. However, they are also associated with abnormalities in glucose/lipid metabolism and body fat distribution. Further studies are needed to better define the pathogenesis of PI-associated metabolic and body fat changes and their potential treatment.

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Figure 1. A schema for the development of HIV/PI-associated lipodystrophy and its associated adverse effects

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; FFA, free fatty acids; HIV, human immunodeficiency virus; PI, protease inhibitor; ROS, reactive oxygen species; TG, triglyceride.

Table 1

Characteristics of available protease inhibitors[6 11 17, 18].

Drug generation	Protease inhibitors	Recommended Dosage[a]	Absorption t_{max} (h)	Protein binding (%)	Plasma $t_{1/2}$ (h)	Metabolism: CYP450
1st	Saquinavir[b]	1000/r100 mg BID	1–2	97	5	Renal+CYP3A4
	Indinavir[b]	800/r100 mg BID	1	61	1.5–2	Renal+CYP3A4
	Ritonavir	600 mg BID	3	98–99	3–5	Renal+CYP3A and 2D6
	Nelfinavir	1250 mg BID	3	≥98	5–6	Renal+CYP3A and 2C19
2nd	Lopinavir[b]	400/r100 BID or 800/r100 QD	5	98–99	5–6	Renal+CYP3A
	Fosamprenavir[b]	700/r100 mg BID	2	90	7–12	Renal+CYP3A
	Atazanavir[b]	300/r100 mg QD	2	86	7	Renal+CYP3A
3rd	Darunavir[b]	800/r100 mg QD	1–4	94	10–15	Renal+CYP3A
	Tipranavir[b]	500/r200 mg BID	3	99	6	Renal+CYP3A

[a] Adapted from: Panel on Antiretroviral Guidelines for Adults and Adolescents

[b] Ritonavir boosted × 1–2; BID, twice a day; TDS, three times a day; QD, once-daily dosing

Table 2

Protease inhibitor clinical trials in drug-naïve HIV patients.

Trial	Authors	Drugs	Patients (in each arm)	Outcome
MaxCmin2[40]	Dragsted et al	SQV/r vs. LPV/r	161/133	Better antiretroviral effects, lower virological failure and treatment discontinuation rates of LPV/r compared with SQV/r
M97–720[41]	Murphy et al	LPV/r	100	59% patients (ITT) had <50 copies/ml plasma HIV-1 RNA through 7 years
KLEAN[37]	Eron et al	fAPV/r vs. LPV/r	434/444	Similar antiretroviral efficacy, safety, tolerability, and emergence of resistance of fAPV compared to LPV/r
CASTLE[38]	Molina et al	ATV/r vs. LPV/r	440/443	Similar antiretroviral efficacy, less GI toxicity, and better lipid and safety profiles with ATV/r
SWAN[42]	Gatell et al	ATV/r vs. other PI	278/141	Better virologic suppression, a comparable safety profile, and improved lipid parameters with ATV/r
RESIST-3[43]	Hicks et al	TPV/r vs. other PI	746/737	Better virological and immunological responses over 48 weeks with TPV/r compared to control PI
POWER 1–2[44]	Clotet et al	DRV/r vs. other PI	131/124	Favorable safety and tolerability, better efficacy at 48 weeks with DRV/r compared to control PI
ARTEMIS[39]	Ortiz et al	DRV/r vs. LPV/r	343/346	Non-inferiority of DRV/r vs. LPV/r at 48 weeks, with a more favorable safety profile
TITAN[45]	Madruga et al	DRV/r vs. LPV/r	298/297	Non-inferiority of DRV/r monotherapy vs. LPV/r
MONET[46]*	Arribas et al	DRV/r monotherapy vs. triple	127/128	Non-inferiority of DRV/r monotherapy vs. triple ART

SQV/r, Saquinavir/ritonavir; LPV/r, Lopinavir/ritonavir; fAPV/r, Fosamprenavir/ritonavir; ATV/r, Atazanavir/ritonavir; TPV/r, Tipranavir/ritonavir; DRV/r, Darunavir/ritonavir; ITT, intention-to-treat, ART, antiretroviral treatment.

Trials: **MaxCmin2**, open-label, randomized, multicenter, comparative trial evaluating the safety and efficacy of lopinavir/ritonavir vs. saquinavir/ritonavir; **M97–720**, open-label, follow-up of prospective, randomized, multicenter trial evaluating the efficacy and tolerability of lopinavir/ritonavir in combination with stavudine and lamivudine; **KLEAN** (Kaletra versus Lexiva with Epivir and Abacavir in ART-Naive patients), open-label, randomized, non-inferiority study comparing fosamprenavir/ritonavir vs. lopinavir/ritonavir; **CASTLE**, open-label, randomized, multicenter, non-inferiority study evaluating the safety and efficacy of atazanavir/ritonavir vs. lopinavir/ritonavir; **SWAN** (Switch to Another Protease Inhibitor), open-label, comparative trial evaluating the safety and efficacy of atazanavir/ritonavir vs. comparator PI; **RESIST-3** (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients With Tipranavir), open-label, randomized, multinational, phase III study evaluating the efficacy of tipranavir/ritonavis vs. other PI; **POWER 1–2** (Performance of TMC114/r When Evaluated in Treatment-Experienced Patients with PI Resistance) open-label, randomized, multinational, phase III study evaluating the efficacy and safety of darunavir/ritonavir vs. currently available PIs; **ARTEMIS** (AntiRetroviral Therapy with TMC114 ExaMined In naive Subjects) open-label, randomized, comparative trial evaluating the efficacy and safety of darunavir/ritonavir vs. lopinavir/ritonavir; **TITAN** (TMC114/r In Treatment-experienced pAtients Naïve to lopinavir) open-label, randomized, international, comparative trial evaluating the safety and efficacy of darunavir/ritonavir vs. lopinavir/ritonavir; **MONET** (Montreal Ottawa New Emerging Team), open-label, randomized, phase III non-inferiority study evaluating safety and efficacy of darunavir/ritonavir (monotherapy) vs. two nucleoside analogues and darunavir/ritonavir (triple therapy arm).