Adipocyte 4:1, 55–59; January/February/March 2015; © 2015 Taylor & Francis Group, LLC

Viral mechanisms of adipose dysfunction: lessons from HIV-1 Vpr

N Agarwal[1] and A Balasubramanyam[1,2,*]

[1]Translational Metabolism Unit; Diabetes Research Center; Division of Diabetes; Endocrinology and Metabolism; Baylor College of Medicine; Houston, TX USA;
[2]Endocrine Service; Ben Taub General Hospital; Houston, TX USA

HIV-associated lipodystrophy is a heterogeneous, evolving condition associated with fundamental defects in adipose tissue differentiation, turnover and function. Although many antiretroviral drugs can affect adipose tissues adversely, clinical evidence suggests that factors associated with the virus per se could play a role. We have focused on the possibility that an HIV accessory protein, viral protein R (Vpr) could dysregulate metabolically critical transcription factors to cause the adipose dysfunction. In a recent study published in *Science Translational Medicine,* we utilized 2 animal models to show that Vpr, produced in tissues that sequester HIV after antiretroviral therapy, can act in a paracrine or endocrine fashion to disrupt adipocyte differentiation and function by inhibiting PPARγ target gene expression and activating glucocorticoid target gene expression. The phenotypic consequences included many features typical of the human syndrome, including accelerated lipolysis, increased macrophage infiltration in adipose tissue, diminished size of white adipose depots and hepatic steatosis. In this commentary, we summarize the background, results, and implications of these studies, and raise important questions for future investigation. More broadly, these studies suggest that chronic viral infections may be a causative factor in the pathogenesis of some forms of lipid metabolic disease, insulin resistance, and diabetes.

Keywords: cell-cycle arrest, fat oxidation, glucocorticoid receptor (GR), HIV-1, hepatosteatosis, insulin resistance, lipodystrophy, lipolysis, metabolic disorder, peroxisome proliferator activated receptor (PPAR), viral infection, Vpr

*Correspondence to: Ashok Balasubramanyam; Email: ashokb@bcm.edu

Submitted: 04/04/2014

Revised: 07/07/2014

Accepted: 07/07/2014

http://dx.doi.org/10.4161/adip.29852

Commentary to: Agarwal N, Iyer D, Patel SG, Sekhar RV, Phillips TM, Schubert U, Oplt T, Buras ED, Samson SL, Couturier J, Lewis DE, Rodriguez-Barradas MC, Jahoor F, Kino T, Kopp JB, Balasubramanyam A. HIV-1 Vpr induces adipose dysfunction in vivo through reciprocal effects on PPAR/GR co-regulation. Sci Transl Med 2013; 5:213ra164; PMID: 24285483; http://dx.doi.org/10.1126/scitranslmed.3007148

Obesity, primarily a condition of dysfunctional adipose tissue, is the traditional starting point for translational investigations into adipose defects in humans. However, the phenotypic heterogeneity and etiological complexity of human obesity render it a difficult model to dissect pathophysiologic pathways and identify specific molecular defects. The human lipodystrophy syndromes (conditions of generalized or regional fat loss with or without fat expansion in some areas) are somewhat more tractable to specific etiologic analysis, and could be useful models to uncover primary adipocyte-specific defects that in turn could shed light on adipocyte biology and on pathways that may be disrupted in "common" obesity. Over a dozen rare lipodystrophic syndromes have yielded to genetic analyses, and have proven to have a monogenic cause.[1] The degree of complexity is increased when one considers the acquired lipodystrophic syndromes; for one thing, "lipodystrophy" is to some extent in the eye of the beholder, and subtle forms may go unnoticed against the powerful secular trend toward overnutrition-related adipose expansion. For another, the acquired lipodystrophy syndromes tend to have multiple phenotypes with ranges of severity depending on the timing, chronicity, and reversibility of the aggravating causes.[2]

HIV-associated lipodystrophy is a striking, widespread but phenotypically heterogeneous and highly variable acquired lipodystrophic syndrome that first came to clinical notice when protease inhibitor drugs became the backbone of HIV therapy in the late 1990s.[3-8] Importantly, the anthropomorphic changes described as "fat redistribution" were associated with markers of dyslipidemia, vascular inflammation, insulin resistance and accelerated atherosclerosis; the prevalence of these "metabolic" defects spread well beyond patients with visible or quantifiable adipose depot changes. These adipose

and lipid metabolic defects were initially attributed to adverse effects of the PI drugs, but, with some variations, they were also noted in association with nucleoside reverse transcriptase agents, and, to subtler degrees, with drugs of other classes and modes of action. Now, in the era of the fourth or fifth generations of antiretroviral drugs, it is clear that in addition to adverse drug effects, there are important roles for persistent HIV-1 per se and for the associated chronic immune/inflammatory responses in the pathophysiology of the adipose and metabolic disturbances.[9-12]

Biochemical evidence for a fundamental defect in adipose tissue function in HIV patients came from human metabolic studies indicating that accelerated lipolysis with defective oxidation of the released fatty acids in the fasted state, and extremely poor clearance of dietary fat in the fed state, are characteristic features of HIV-associated metabolic disease.[13–15] These manifestations pointed to a fundamental dysregulation of adipocyte enzymes such as hormone sensitive lipase and lipoprotein lipase,[16-20] raising the likelihood of specific regulatory defects that could explain abnormalities of multiple enzymes and pathways. Biopsy studies of lipoatrophic regions of subcutaneous fat in HIV patients demonstrated a high degree of apoptosis, together with diminished expression of an array of genes of adipocyte differentiation, including PPARγ [21-23]; this placed the fundamental lesions, at least in subcutaneous fat, within pathways of preadipocyte differentiation and adipocyte apoptosis. Clues as to the fundamental lesions in hypertrophic visceral fat were scarce due to a paucity of studies of those depots, while biopsies and functional studies of regional fat accumulation, such as in the cervical region, indicated a possible transformation of pockets of WAT to a beige or brown fat phenotype.[24] Collectively, these data indicated that the adipose defects likely occur in both preadipocytes and adipocytes, due to defects in transcriptional regulation of differentiation as well as in enzymatic activities of function, and differentially in various adipose depots.

In the attempt to find common factors that would cause these pleiotropic disturbances in adipose regulation, we were intrigued by elegant work from the laboratories of Dr. Kino, Chrousos and Kopp at the NIH, demonstrating that viral protein R (Vpr), an HIV-1 accessory protein, could function in vitro as a potent co-activator of the glucocorticoid receptor and a co-repressor of PPARγ.[25-27]. Furthermore, Vpr could induce G2/M cell-cycle arrest and apoptosis.[28] Importantly—since lipodystrophy and metabolic aberrations are most apparent in HIV patients on apparently effective antiretroviral therapy with undetectable plasma viral load—Vpr had the characteristics of a hormone, i.e., it could be released from HIV-1-infected cells (including replication-deficient HIV-1) and despite inhibition of viral replication by protease inhibitors,[28] circulate independently of intact HIV-1,[29] and transduce a range of cells in a receptor-and energy-independent manner.[27,29] These features suggested the following hypothesis—Vpr released from HIV-1-infected immune cells within reservoirs in ART-treated patients could act as endocrine or paracrine effectors, transduce adipose cells to promote glucocorticoid sensitivity and downregulate PPARγ, and produce the characteristic biochemical and clinical features.

In work published recently in *Science Translational Medicine*,[30] we first demonstrated that Vpr is present in the serum of both treated and untreated HIV patients, with no relation to plasma viral load, then utilized 2 mouse models to demonstrate mechanisms whereby Vpr can disrupt adipose differentiation and function in vivo. The first (transgenic) model was designed to investigate whether Vpr expression in the metabolic tissues of interest can cause characteristic HIV-associated metabolic defects, and the second (pharmacologic) model was designed to investigate whether virion-free Vpr in the circulation is sufficient to cause these defects in adipose cells and hepatocytes.

The two mouse models displayed a very similar phenotype that substantially recapitulated the cardinal defects in HIV patients. The Vpr mice demonstrated increased lipolysis with blunted fat oxidation, diminished WAT mass with increased macrophage infiltration, blunted expression of PPARγ-target genes regulating adipocyte differentiation and function (*Pparγ, Adiponectin, Ap2, Cap, Cd36, Glut4, Lpl, Perilipin*) but increased expression of GR-target genes regulating lipolysis (*Atgl, Hsl*) in perigonadal and inguinal fat depots, and decreased circulating levels of adiponectin (total and HMW) and aP2. Moreover, Vpr was present in the serum of the transgenic mice, indicating that Vpr expressed within cells is released into the circulation.

Several details of the specific cellular mechanisms revealed by these models provide insights into how a nuclear-acting pathogenic factor could produce different effects in different tissues, and even in different adipose depots. For example, within the perigonadal adipose depot (analogous to visceral fat in humans), protein expression of adipocyte triglyceride lipase (ATGL, which catalyzes the hydrolysis of the first fatty acid in triglyceride) was markedly increased, reflecting Vpr's co-activation of its gene transcription via the glucocorticoid receptor. ATGL protein was also increased within the inguinal fat depot (analogous to subcutaneous adipose tissue in humans), though much less than in the perigonadal fat. However the level of the active (phospho-Ser563) form of hormone sensitive lipase (HSL, which catalyzes the hydrolysis of the second fatty acid in triglyceride) was altered by Vpr in opposite directions in these 2 depots—— increased in perigonadal fat but decreased in inguinal fat. This discordance reveals a potential mechanism for the observation that in conditions of generalized adipose dysfunction such as obesity, lipolysis is greater in visceral compared to subcutaneous fat [31]; glucocorticoid "effectiveness," e.g. by activation of 11-β hydroxysteroid dehydrogenase type 1, might vary in these depots due to differential expression of the rate-determining lipolytic enzymes, and result in a greater flux of fatty acids directly into the portal vein than into systemic venous effluents.[32] It also suggests that whole body hyperlipolysis could result in greater release of diglycerides in inguinal than in perigonadal fat. Recent work has suggested that products of lipolysis play an important chemotactic role in the entry of monocytes into adipose tissues [33]; we have found that T cells

infiltrate the inguinal fat of Vpr mice in greater numbers than in perigonadal fat, and it is possible that a higher concentration of diglycerides in the former depot plays a role in this phenomenon.

A common finding, especially among men with HIV infection on HAART, is that lipoatrophy in subcutaneous adipose tissues is not matched by similar loss of fat in visceral adipose depots—indeed the latter are frequently expanded.[3-8] The Vpr mouse models display diminution of fat mass in both inguinal ("subcutaneous") and perigonadal ("visceral") depots, which is at odds with the pattern in humans. A careful gene expression study by Gallego-Escuerdo et al, utilizing human biopsy samples from both subcutaneous and visceral fat depots of antiretroviral-treated HIV-1 infected patients, has explored the mechanistic basis for this depot difference.[34] These investigators found that while expression of adipogenic genes such as PPARγ was diminished in subcutaneous fat, it was unchanged in visceral fat; this was accompanied by milder increases in proinflammatory cytokine gene expression in the visceral compared to the subcutaneous fat. These findings suggest that in the context of human infection with HIV-1, the effects of Vpr on visceral fat could be modulated by factors such as immune alterations associated with gut-lymphoid tissues, or by transcriptional co-regulators or micro-RNA's specific to visceral adipose tissue.[35-37] The possibility that Vpr could modulate estrogen receptor signaling, which may also vary in different adipose depots, is discussed below.

A provocative observation in the Vpr mice was the rapid development of hepatic steatosis within a few weeks of induction of Vpr expression or synthetic Vpr administration. This is of great interest in view of the high prevalence of non-alcoholic fatty liver disease among HIV patients (currently estimated at 30–35% of mono-infected patients, i.e., those without concomitant hepatitis B or C infection).[38–43] Accelerated lipolysis in visceral adipose tissue undoubtedly contributes to the fatty liver phenotype, but we also found evidence pointing to additional mechanisms: diminished oxidative disposal of fatty acids and defective VLDL-triglyceride export. Evidence for the former was found in blunted expression of hepatic genes regulating fat oxidation (*Pparα, Cpt1, Lcad, Aox*), and for the latter in decreased expression of *Mtp1*, encoding microsomal triglyceride transfer protein which is critical for hepatic VLDL-TG export. We are currently performing experiments to obtain biochemical support for these findings; for the present, the interesting fact is that all of these genes are regulated by PPARα, hence it appears that Vpr co-represses PPARα in liver just as it does PPARγ in adipose tissues. Collectively, these data indicate that Vpr may be a relatively promiscuous co-regulator of an array of metabolically important transcription factors, at least in part through direct interactions via its LXXLL motif.[25-27] As with the reciprocal effects upon GR compared to PPARg/PPARa, the coregulation could be positive or negative. Indeed, the Kopp lab has recently shown that Vpr also interacts with another PPAR family member, PPARβ/δ - however, the effect in this instance is to increase PPAR response element-driven transcriptional activity, with a consequent reduction in the activity of the pyruvate dehydrogenase complex in HepG2 cells and increase in mitochondrial oxygen consumption.[44] This effect could contribute to impaired hepatic energy metabolism (diminished oxidative phosphorylation) and increased energy expenditure in HIV patients. Very recent (unpublished) work in our lab suggests that Vpr could also co-regulate liver X receptor-α (LXRα), with important consequences for altered rates of hepatic lipogenesis.

Another interesting observation, currently still preliminary, relates to gender differences in the Vpr mouse phenotype. Male mice, as noted above, have decreased WAT mass. Female mice, on the other hand, appear to manifest expansion of most WAT depots compared to wild-type littermates. This is intriguing because in many cross-sectional analyses of HIV patient cohorts, lipohypertrophy is more prevalent in women than in men [45-51] (although the longitudinal FRAM Study suggested that progressive peripheral fat loss also occurs in HIV-infected women, and that increased visceral fat accumulation may be restricted to women without peripheral lipoatrophy[52]). These preliminary findings raise the possibility that the estrogen receptor may be yet another transcription factor prone to dysregulation by Vpr.

Despite the intriguing results of these targeted studies, it is clear that heterogeneous manifestations of the HIV-associated lipodystrophy syndrome represent the consequences of multiple, interacting, temporally evolving factors that include HIV-1 per se, immune responses and the undeniable effects of antiretroviral drugs. It is likely, as some investigators have proposed,[53] that products of HIV-1 infection initiate a "first wave" of alterations in adipose tissue that is amplified by antiretroviral toxicity and ultimately results in HIV-1 lipodystrophy.

In conclusion, our reported and ongoing studies in the Vpr mouse models and cellular investigations reveal fresh approaches into the study of acquired disorders of adipose dysfunction, and point to specific areas of future investigation. The most significant concept is that a product of a chronic viral infection can co-opt key transcriptional regulators of energy metabolism to give rise to lipodystrophy. Is this is generalizable concept, i.e., could this occur in the context of other viral or parasitic infections? Much work remains be done to establish this concept. First and foremost, it will be important to confirm, through biopsy studies correlated with organ specific function, that Vpr is a significant pathophysiologic mechanism in HIV infected patients. In parallel with this effort is the need to understand Vpr mechanisms underlying fatty liver disease and the sex difference in the lipodystrophic phenotype. Studies to address these questions are under way.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Hegele RA, Joy TR, Al-Attar SA, Rutt BK. Thematic review series: Adipocyte Biology. Lipodystrophies: windows on adipose biology and metabolism. J Lipid Res 2007; 48:1433-44; PMID:17374881; http://dx.doi.org/10.1194/jlr.R700004-JLR200
2. Huang-Doran I, Sleigh A, Rochford JJ, O'Rahilly S, Savage DB. Lipodystrophy: metabolic insights from a rare

disorder. J Endocrinol 2010; 207:245-55; PMID:20870709; http://dx.doi.org/10.1677/JOE-10-0272
3. Shevitz A, Wanke CA, Falutz J, Kotler DP. Clinical perspectives on HIV-associated lipodystrophy syndrome: an update. Aids 2001; 15:1917-30; PMID:11600819; http://dx.doi.org/10.1097/00002030-200110190-00003
4. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. "Buffalo hump" in men with HIV-1 infection. Lancet 1998; 351:867-70; PMID:9525364; http://dx.doi.org/10.1016/S0140-6736(97)11443-X
5. Gougeon ML, Penicaud L, Fromenty B, Leclercq P, Viard JP, Capeau J. Adipocytes targets and actors in the pathogenesis of HIV-associated lipodystrophy and metabolic alterations. Antivir Ther 2004; 9:161-77; PMID:15134178
6. Giralt M, Domingo P, Guallar JP, Rodriguez de la Concepcion ML, Alegre M, Domingo JC, Villarroya F. HIV-1 infection alters gene expression in adipose tissue, which contributes to HIV- 1/HAART-associated lipodystrophy. Antivir Ther 2006; 11:729-40; PMID:17310817
7. Guallar JP, Gallego-Escuredo JM, Domingo JC, Alegre M, Fontdevila J, Martinez E, Hammond EL, Domingo P, Giralt M, Villarroya F. Differential gene expression indicates that 'buffalo hump' is a distinct adipose tissue disturbance in HIV-1-associated lipodystrophy. Aids 2008; 22:575-84; PMID:18316998; http://dx.doi.org/10.1097/QAD.0b013e3282f56b40
8. Milinkovic A. HIV-associated lipodystrophy syndrome. Coll Antropol 2006; 30 Suppl 2:59-62; PMID:17508476
9. Balasubramanyam A, Sekhar RV, Jahoor F, Jones PH, Pownall HJ. Pathophysiology of dyslipidemia and increased cardiovascular risk in HIV lipodystrophy: a model of 'systemic steatosis'. Curr Opin Lipidol 2004; 15:59-67; PMID:15166810; http://dx.doi.org/10.1097/00041433-200402000-00011
10. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1989; 86:27-31; PMID:2910092; http://dx.doi.org/10.1016/0002-9343(89)90225-8
11. Visnegarwala F, Raghavan SS, Mullin CM, Bartsch G, Wang J, Kotler D, Gibert CL, Shlay J, Grunfeld C, Carr A, et al. Sex differences in the associations of HIV disease characteristics and body composition in antiretroviral-naive persons. Am J Clin Nutr 2005; 82:850-6; PMID:16210716
12. Bacchetti P, Gripshover B, Grunfeld C, Heymsfield S, McCreath H, Osmond D, Saag M, Scherzer R, Shlipak M, Tien P, et al. Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr 2005; 40:121-31; PMID:16186728; http://dx.doi.org/10.1097/01.qai.0000182230.47819.aa
13. Sekhar RV, Jahoor F, White AC, Pownall HJ, Visnegarwala F, Rodriguez-Barradas MC, Sharma M, Reeds PJ, Balasubramanyam A. Metabolic basis of HIV-lipodystrophy syndrome. Am J Physiol Endocrinol Metab 2002; 283:E332-7; PMID:12110539
14. Reeds DN, Mittendorfer B, Patterson BW, Powderly WG, Yarasheski KE, Klein S. Alterations in lipid kinetics in men with HIV-dyslipidemia. Am J Physiol Endocrinol Metab 2003; 285:E490-7; PMID:12746213
15. Hadigan C, Borgonha S, Rabe J, Young V, Grinspoon S. Increased rates of lipolysis among human immunodeficiency virus-infected men receiving highly active antiretroviral therapy. Metabolism 2002; 51:1143-7; PMID:12200758; http://dx.doi.org/10.1053/meta.2002.34704
16. Zechner R, Kienesberger PC, Haemmerle G, Zimmermann R, Lass A. Adipose triglyceride lipase and the lipolytic catabolism of cellular fat stores. J Lipid Res 2009; 50:3-21; PMID:18952573; http://dx.doi.org/10.1194/jlr.R800031-JLR200
17. Zimmermann R, Lass A, Haemmerle G, Zechner R. Fate of fat: the role of adipose triglyceride lipase in lipolysis. Biochim Biophys Acta 2009; 1791:494-500; PMID:19010445; http://dx.doi.org/10.1016/j.bbalip.2008.10.005
18. Chow DC, Tasaki A, Ono J, Shiramizu B, Souza SA. Effect of extended-release niacin on hormone-sensitive lipase and lipoprotein lipase in patients with HIV-associated lipodystrophy syndrome. Biologics 2008; 2:917-21; PMID:19707470
19. Shen WJ, Yu Z, Patel S, Jue D, Liu LF, Kraemer FB. Hormone-sensitive lipase modulates adipose metabolism through PPARgamma. Biochim Biophys Acta; 1811:9-16; PMID:20950707
20. Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E, Sul HS. Regulation of lipolysis in adipocytes. Annu Rev Nutr 2007; 27:79-101; PMID:17313320; http://dx.doi.org/10.1146/annurev.nutr.27.061406.093734
21. Domingo P, Matias-Guiu X, Pujol RM, Francia E, Lagarda E, Sambeat MA, Sharma M, Reeds PJ, Balasubramanyam A. Subcutaneous adipocyte apoptosis in HIV-1 protease inhibitor-associated lipodystrophy. Aids 1999; 13:2261-7; PMID:10563711; http://dx.doi.org/10.1097/00002030-199911120-00008
22. Domingo P, Vidal F, Domingo JC, Veloso S, Sambeat MA, Torres F, Sirvent JJ, Vendrell J, Matias-Guiu X, Richart C, et al. Tumour necrosis factor alpha in fat redistribution syndromes associated with combination antiretroviral therapy in HIV-1-infected patients: potential role in subcutaneous adipocyte apoptosis. Eur J Clin Invest 2005; 35:771-80; PMID:16313254; http://dx.doi.org/10.1111/j.1365-2362.2005.01576.x
23. Jan V, Cervera P, Maachi M, Baudrimont M, Kim M, Vidal H, Girard PM, Levan P, Rozenbaum W, Lombès A, et al. Altered fat differentiation and adipocytokine expression are inter-related and linked to morphological changes and insulin resistance in HIV-1-infected lipodystrophic patients. Antivir Ther 2004; 9:555-64; PMID:15456087
24. Torriani M, Fitch K, Stavrou E, Bredella MA, Lim R, Sass CA, Cypess AM, Grinspoon S. Deiodinase 2 expression is increased in dorsocervical fat of patients with HIV-associated lipohypertrophy syndrome. J Clin Endocrinol Metab 2012; 97:E602-7; PMID:22259052; http://dx.doi.org/10.1210/jc.2011-2951
25. Kino T, Gragerov A, Kopp JB, Stauber RH, Pavlakis GN, Chrousos GP. The HIV-1 virion-associated protein vpr is a coactivator of the human glucocorticoid receptor. J Exp Med 1999; 189:51-62; PMID:9874563; http://dx.doi.org/10.1084/jem.189.1.51
26. Kino T, Gragerov A, Slobodskaya O, Tsopanomichalou M, Chrousos GP, Pavlakis GN. Human immunodeficiency virus type 1 (HIV-1) accessory protein Vpr induces transcription of the HIV-1 and glucocorticoid-responsive promoters by binding directly to p300/CBP coactivators. J Virol 2002; 76:9724-34; PMID:12208951; http://dx.doi.org/10.1128/JVI.76.19.9724-9734.2002
27. Shrivastav S, Kino T, Cunningham T, Ichijo T, Schubert U, Heinklein P, Chrousos GP, Kopp JB. Human immunodeficiency virus (HIV)-1 viral protein R suppresses transcriptional activity of peroxisome proliferator-activated receptor {gamma} and inhibits adipocyte differentiation: implications for HIV-associated lipodystrophy. Mol Endocrinol 2008; 22:234-47; PMID:17932108; http://dx.doi.org/10.1210/me.2007-0124
28. Poon B, Grovit-Ferbas K, Stewart SA, Chen IS. Cell cycle arrest by Vpr in HIV-1 virions and insensitivity to antiretroviral agents. Science 1998; 281:266-9; PMID:9657723; http://dx.doi.org/10.1126/science.281.5374.266
29. Sherman MP, Schubert U, Williams SA, de Noronha CM, Kreisberg JF, Henklein P, Greene WC. HIV-1 Vpr displays natural protein-transducing properties: implications for viral pathogenesis. Virology 2002; 302:95-105; PMID:12429519; http://dx.doi.org/10.1006/viro.2002.1576
30. Agarwal N, Iyer D, Patel SG, Sekhar RV, Phillips TM, Schubert U, Oplt T, Buras ED, Samson SL, Couturier J, et al. HIV-1 Vpr induces adipose dysfunction in vivo through reciprocal effects on PPAR/GR Co-regulation. Sci Transl Med 2013; 5:213ra164; PMID:24285483; http://dx.doi.org/10.1126/scitranslmed.3007148
31. Arner P. Differences in lipolysis between human subcutaneous and omental adipose tissues. Ann Med 1995; 27:435-8; PMID:8519504; http://dx.doi.org/10.3109/07853899509002451
32. Chapman K, Holmes M, Seckl J. 11beta-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev 2013; 93:1139-206; PMID:23899562; http://dx.doi.org/10.1152/physrev.00020.2012
33. Kosteli A, Sugaru E, Haemmerle G, Martin JF, Lei J, Zechner R, Ferrante AW Jr. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. J Clin Invest 2010; 120:3466-79; PMID:20877011; http://dx.doi.org/10.1172/JCI42845
34. Gallego-Escuredo J, Villarroya J, Domingo P, Targarona E, Alegre M Domingo JC, Villarroya F, Giralt M. Differentially altered molecular signature of visceral adipose tissue in HIV-1–associated lipodystrophy. JAIDS 2013; 64:142-8; PMID:23714743
35. Klöting N, Berthold S, Kovacs P, Schon MR, Fasshauer M, Ruschke K, Stumvoll M, Blüher M. MicroRNA expression in human omental and subcutaneous adipose tissue. PLoS One 2009; 4(3):e4699; PMID:19259271; http://dx.doi.org/10.1371/journal.pone.0004699
36. Ortega FJ, Moreno-Navarrete JM, Ribas V, Esteve E, Rodriguez-Hermosa JI, Ruiz B, Peral B, Ricart W, Zorzano A, Fernández-Real JM. Subcutaneous fat shows higher thyroid hormone receptor-alpha1 gene expression than omental fat. Obesity (Silver Spring) 2009; 17:2134-41; PMID:19360007; http://dx.doi.org/10.1038/oby.2009.110
37. Ortega FJ, Moreno-Navarrete JM, Pardo G, Sabater M, Hummel M, Ferrer A, Rodriguez-Hermosa JI, Ruiz B, Ricart W, Peral B, et al. MiRNA expression profi le of human subcutaneous adipose and during adipocyte differentiation. PLoS One 2010; 5(2):e9022; PMID:20126310; http://dx.doi.org/10.1371/journal.pone.0009022
38. Hadigan C, Liebau J, Andersen R, Holalkere NS, Sahani DV. Magnetic resonance spectroscopy of hepatic lipid content and associated risk factors in HIV infection. J Acquir Immune Defic Syndr 2007; 46:312-7; PMID:17721396; http://dx.doi.org/10.1097/QAI.0b013e3181568cc2
39. Lemoine M, Serfaty L, Capeau J. From nonalcoholic fatty liver to nonalcoholic steatohepatitis and cirrhosis in HIV-infected patients: diagnosis and management. Curr Opin Infect Dis 2012; 25:10-6; PMID:22183113; http://dx.doi.org/10.1097/QCO.0b013e32834ef599
40. Blackard JT, Welge JA, Taylor LE, Mayer KH, Klein RS, Celentano DD, Jamieson DJ, Gardner L, Sherman KE. HIV mono-infection is associated with FIB-4 - A noninvasive index of liver fibrosis - in women. Clin Infect Dis 2011; 52:674-80; PMID:21248367; http://dx.doi.org/10.1093/cid/ciq199
41. Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, Fiocchi F, Zona S, Loria P, Esposito R, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis 2008; 47:250-7; PMID:18532884; http://dx.doi.org/10.1086/589294
42. Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, Goodman Z, Parker R, Lifson A, Capozza T, et al. Nonalcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr 2009; 50:464-73; PMID:19225402; http://dx.doi.org/10.1097/QAI.0b013e318198a88a
43. Mendeni M, Foca E, Gotti D, Ladisa N, Angarano G, Albini L, Castelnuovo F, Carosi G, Quiros-Roldan E, Torti C. Evaluation of liver fibrosis: concordance analysis between noninvasive scores (APRI and FIB-4) evolution and predictors in a cohort of HIV-infected patients without hepatitis C and B infection. Clin Infect Dis 2011; 52:1164-73; PMID:21467023; http://dx.doi.org/10.1093/cid/cir071

44. Shrivastav S, Zhang L, Okamoto K, Lee H, Lagranha C, Abe Y, Balasubramanyam A, Lopaschuk GD, Kino T, Kopp JB. HIV-1 Vpr enhances PPARβ/δ-mediated transcription, increases PDK4 expression, and reduces PDC activity. Mol Endocrinol. 2013; 27:1564-76; PMID:23842279
45. Jacobson DL, Knox T, Spiegelman D, Skinner S, Gorbach S, Wanke C. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. Clin Infect Dis 2005; 40:1837-45; PMID:15909274; http://dx.doi.org/10.1086/430379
46. Andany N, Raboud JM, Walmsley S, Diong C, Rourke SB, Rueda S, Rachlis A, Wobeser W, Macarthur RD, Binder L, et al. Ethnicity and gender differences in lipodystrophy of HIV-positive individuals taking antiretroviral therapy in Ontario, Canada. HIV Clin Trials 2011; 12:89-103; PMID:21498152; http://dx.doi.org/10.1310/hct1202-89
47. Heath KV, Chan KJ, Singer J, O'Shaughnessy MV, Montaner JS, Hogg RS. Incidence of morphological and lipid abnormalities: gender and treatment differentials after initiation of first antiretroviral therapy. Int J Epidemiol 2002; 31:1016-20; PMID:12435777; http://dx.doi.org/10.1093/ije/31.5.1016
48. Galli M, Veglia F, Angarano G, Santambrogio S, Meneghini E, Gritti F, Cargnel A, Mazzotta F, Lazzarin A. Gender differences in antiretroviral drug-related adipose tissue alterations. Women are at higher risk than men and develop particular lipodystrophy patterns. J Acquir Immune Defic Syndr 2003; 34:58-61; PMID:14501794; http://dx.doi.org/10.1097/00126334-200309010-00008
49. McComsey G, Rightmire A, Wirtz V, Yang R, Mathew M, McGrath D. Changes in body composition with ritonavir-boosted and unboosted atazanavir treatment in combination with Lamivudine and Stavudine: a 96-week randomized, controlled study. Clin Infect Dis 2009; 48:1323-6; PMID:19302017; http://dx.doi.org/10.1086/597776
50. Gasparotto AS, Sprinz E, Lazzaretti RK, Kuhmmer R, Silveira JM, Basso RP, Pinheiro CA, Silveira MF, Ribeiro JP, Mattevi VS. Genetic polymorphisms in estrogen receptors and sexual dimorphism in fat redistribution in HIV-infected patients on HAART. Aids 2012; 26:19-26; PMID:22011627; http://dx.doi.org/10.1097/QAD.0b013e32834db3ac
51. Cabrero E, Griffa L, Burgos A. Prevalence and impact of body physical changes in HIV patients treated with highly active antiretroviral therapy: results from a study on patient and physician perceptions. AIDS Patient Care STDS 2010; 24:5-13; PMID:20095903; http://dx.doi.org/10.1089/apc.2009.0191
52. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. J Acquir Immune Defic Syndr 2006; 42:562-71; PMID:16837863; http://dx.doi.org/10.1097/01.qai.0000229996.75116.da
53. Caron-Debarle M, Lagathu C, Boccara F, Vigouroux C, Capeau J. HIV-associated lipodystrophy: from fat injury to premature aging. Trends Mol Med 2010; 16:218-29; PMID:20400373; http://dx.doi.org/10.1016/j.molmed.2010.03.002