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Review

The role of glucose and lipid metabolism in the pathogenesis of HIV-1 infection

Clovis S. Palmer[1,2] and Suzanne M. Crowe[1,3,4,*]

[1]Centre for Virology, Burnet Institute, Melbourne, [2]School of Medical Sciences, University of New South Wales, Sydney, [3]Department of Medicine, Monash University, Melbourne, [4]Infectious Diseases Unit, The Alfred, Melbourne, Australia

ABSTRACT

Chronic HIV-1 infection is associated with immune activation and inflammation due at least in part to persistent low levels of circulating pro-inflammatory mediators such as lipopolysaccharide, IL-6, and TNF-α. These mediators can modulate cellular metabolism. Thus cells of the immune system must constantly modify their metabolic phenotype according to their changing functional requirements and their environment. During a viral infection, immune cells increase their nutrient uptake and metabolic activity to mount an antiviral response. Changes in glucose and lipid mobilization and metabolism have emerged as being central to this metabolic response. The chronic exposure of leucocytes to an inflammatory milieu may impose an aberrant nutrient metabolic profile in these cells and lead to reduced cell function. Additionally, both HIV-1 infection and antiretroviral therapy induce changes in systemic levels of adipokines and classical inflammatory cytokines released by adipose tissue that may induce endocrine effects on nutrient uptake and metabolism by leucocytes.

KEYWORDS: HIV-1, lymphocytes, monocytes, macrophage, glucose, Glut1, lipids, cART, metabolism

*Corresponding author: Prof. Suzanne M. Crowe
Centre for Virology, Macfarlane Burnet Institute for Medical Research and Public Health, 85 Commercial Rd., Melbourne 3004, Australia.
crowe@burnet.edu.au

INTRODUCTION

A characteristic feature of the early metabolic activities in mammalian cells in response to stress is an increase in the rate of cellular glucose uptake. Over the past few years the roles of glucose and lipid metabolism on the differentiation and functions of immune cells have been highlighted. During the early phase of an immune response, T cells must amplify their nutrient intake to meet the increased metabolic demands of growth, proliferation and differentiation to promote a robust antiviral response [1]. It is becoming clearer that the functions of lymphocytes and other leucocytes are controlled by their intrinsic metabolic profiles. Hence during T cell activation, increased glucose uptake and metabolism is required for cellular survival and function, the so-called *fuel for function* [2, 3].

Metabolic disturbances during chronic viral infections are complex and involve the interplay between genetic, environmental and therapeutic factors. The interaction between viral infections and metabolic responses has been best studied with hepatitis C virus (HCV) infections [4-8]. In a large prospective study of patients with chronic HCV infection, defects in glucose metabolism including insulin resistance were found in approximately one third of patients without diabetes and were associated with the metabolic syndrome [9, 10]. In turn, the metabolic syndrome and its manifestations have been shown in many studies in HCV-infected patients to be associated with a reduced response to antiviral therapy

[11-15] and impaired anti-HCV T cell-responses [16]. Whilst a direct effect of HIV-1 on nutrient metabolism is less clear, several studies support the contribution of some HIV-1 antiretroviral drugs to the dysregulation of lipid and glucose metabolism [17-22], comprehensively reviewed elsewhere [23-25].

Recent discussions have drawn attention to the emerging field of immunometabolism, which focuses on the interplay between viral infections, obesity, glucose and lipid metabolism and immune processes [26-30]. The adipose tissue has long been linked with the emergence of a cluster of associated diseases such as insulin resistance, hypertension, dyslipidaemia and cardiovascular dysfunction, collectively referred to as the metabolic syndrome. The heightened global obesity epidemic has focussed on adipose tissue as a major player in not only storage and release of triglycerides but also in modulating the immune system. Adipose tissue is composed of white adipose tissue (WAT) and brown adipose tissue (BAT). BAT is predominantly associated with thermogenesis while WAT is associated with endocrine functions and accounts for the largest lipid reservoir in humans. Hence WAT has emerged as a major immune organ secreting bioactive adipokines (hormones and pro-inflammatory cytokines) that have immunomodulatory effects. Inflammation of WAT in obesity results in the recruitment of activated T cells and macrophages. Thus, WAT serves as a reservoir of these inflammatory cells that perpetuate inflammation in WAT and the periphery [31-33].

Uncontrolled HIV-1 replication in untreated HIV-1-positive patients, and low residual viremia during combination antiretroviral therapy (cART), is associated with immune activation and chronic systemic inflammation, characterized by elevated levels of inflammatory or coagulation markers such as C reactive protein, IL-6, TNF-α, D-dimer, and cystatin [34, 35]. This pro-inflammatory state is causally linked to the increased incidence of non-AIDS co-morbidities including cardiovascular disease, non-alcoholic fatty liver disease and other diseases which have no obvious metabolic components, such as renal dysfunction and neurocognitive decline.

This review will first focus on the extent to which the intrinsic metabolic profiles of immune cells may change during HIV-1 infection and how these metabolic changes affect cellular functions. Although this concept is relatively under explored, recent data support a key role of glucose metabolic pathways in CD4+ T cells and monocytic cell lines in supporting HIV-1 production and maintenance of HIV-1 latency [36, 37]. In the context of HIV-1infection this review will bring to the forefront the effects of HIV-1 antiretroviral drugs on adipocytes, lipid and glucose homeostasis. We will outline some plausible mechanisms by which adipokines and altered lipid and glucose metabolism may affect the functions of cells of both the adaptive and innate immune system.

Glucose metabolic responses in T cells

The role of glucose metabolism in T cells during early phase immune responses

A characteristic feature early in HIV-1 infection is immune activation that places large metabolic demands on immune cells as they attempt to counteract the virus. This response comprises both HIV-1 specific metabolic changes and immune effects that include T cell activation, proliferation and effector cytokine production.

The cellular growth, function, and survival of activated T cells depend on a dramatic increase in glucose metabolism to provide cellular fuel. This augmented glucose metabolism is highly regulated and has a profound impact on a sustained antiviral response. Thus, impaired glucose metabolism in T cells has been demonstrated to prevent full effector function, with failure of T cells to proliferate and to maximally express cytokines such as IFN-γ and IL-2 [3]. Impaired glucose metabolism not only acutely inhibits T cell function but also promotes the induction of T cell anergy in Th1 T cells [2, 3]. Despite the presence of alternative metabolic fuels, limiting glucose metabolism in activated T cells results in induction of apoptosis [38-40]. Therefore, since T cells lack transcripts of cytosolic phosphoenolpyruvate carboxykinase (C. Palmer, D. Simar, A. Lloyd and A. Zekry unpublished data), a rate limiting enzyme in gluconeogenesis (a process by which cells synthesize glucose from metabolic precursors), the optimum functioning of glucose uptake machinery becomes critical during T cell activation. As T cells become activated and

undergo clonal expansion they preferentially metabolize glucose to lactate, even in the presence of oxygen levels that is sufficient to support oxidative phosphorylation. This phenomenon is known as the Warberg effect and is also a common feature of cancer cells [41]. The proposed changes in glycolytic metabolism in T cells in response to HIV-1 infection are shown in Figure 1, which builds from a generalized model of metabolic responses during an immune response [1]. There are currently no experimental data to support this metabolic shift in T cells during the acute phase of HIV-1 infection. However, we speculate that in the context of HIV-1 infection a rapid and robust metabolic response may be indispensable for a strong and effective immune response to control the virus. While an early and robust metabolic response is likely a benefit to the host, persistent HIV-1 infection may result in metabolic exhaustion and the subsequent death of immune cells including CD4+ T cells.

Mechanism of glucose uptake in T cells during early immune responses

Glucose is a hydrophilic molecule and is therefore unable to penetrate the lipid bilayer of the cell wall. Therefore, specific transporter proteins are required to facilitate diffusion into cells. The transport of glucose is mediated by two distinct families of sugar transport proteins: facilitative glucose carriers [glucose transporters (Gluts)] and sodium-glucose co-transporters (SGLTs). The Glut family of transporters are best characterized and are highly regulated by physiological cues from their microenvironment. There are currently 13 functionally characterized Gluts, many of which are cell specific, and they are classified into

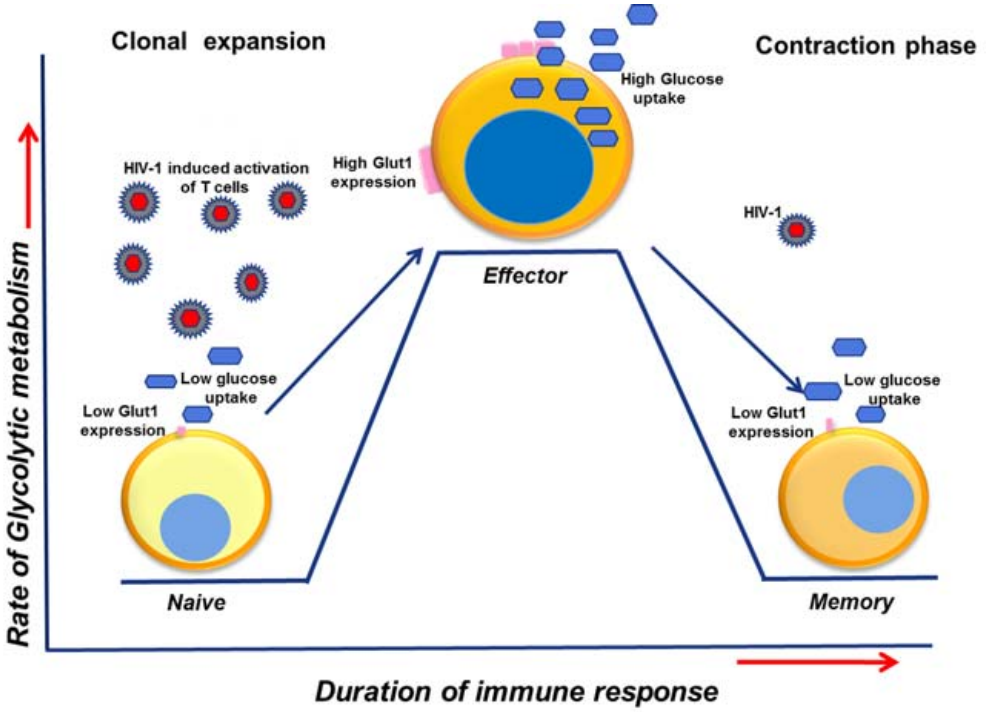

Figure 1. A proposed model of glucose transporter 1 (Glut1) expression and glucose uptake during an immune response to HIV-1 infection and the return to basal Glut1 expression and glucose uptake during the transition from effector to memory T cells. Naive quiescent T cells meet their basal energy demands through the expression of low levels of Glut1 and other nutrient transporters. Upon activation, naïve T cells become highly proliferative and functional and increase Glut1 expression to maintain their energy requirements. Following clonal expansion and viral control, effector cells differentiate into long-lived memory T cells and revert to their basal levels of Glut1 expression and nutrient uptake.

three distinct groups, class I, II and III. The high affinity class I transporters Glut1, Glut3 and Glut4 are widely and abundantly expressed in the body, although Glut4 is preferentially expressed in insulin sensitive tissues such as skeletal muscle and WAT. Glut1 and Glut3 are the predominant isoforms on lymphocytes but Glut1 has attracted more attention in T cell biology because it is more abundantly expressed on these cells than Glut3. Furthermore, the post-transcriptional regulation of Glut1 is highly responsive to immunological signals such as T cell receptor (TCR) activation, mitogens and growth cytokines [42-44].

The early phase of the immune response to HIV-1 infection involves the recognition of HIV-1 antigens by immune cells via antigen presentation and activation of the TCR complex, which engages CD3 and CD28 on the cell surface membrane. However, experiments which involve artificial ligation of the TCR with antibodies against CD3 and CD28 suggests that full T cell activation is dependent on additional environmental signals derived from the inflammatory environment, such as the binding of interleukins to their receptors. This triggers activation predominantly of phosphoinositide 3-kinase (PI3K) and the mammalian target of rapamycin (mTOR) pathways, resulting in heightened translocation of Glut1 from the cytoplasm to the cell surface to facilitate glucose uptake (Figure 2). Subsequently, an increase in glycolytic metabolism occurs, to support T cell proliferation and survival as well as antiviral cytokine secretion and other antiviral responses [38, 45-48]. Some glucose molecules are shuttled to the pentose phosphatase shunt to generate metabolic intermediates for phospholipid and DNA synthesis. Other less characterized signalling and metabolic enzymes that are implicated in T cell activation and glucose uptake by T cells are the extracellular signal-regulated kinase (ERK) [49], signal transducer and activator of transcription 5 (STAT5) [50], some MAPKinases [51] and hexokinase II [52]. These signalling pathways may eventually cooperate or converge with the PI3K and mTOR pathways [53]. It is unknown whether HIV-1 directly or indirectly targets these pathways to disrupt optimal T cell activation and immunological responses. However, it is more evident that HIV-1 infection hyper-activates CD4+ T cells, potentially making them preferential targets for HIV-1 infection.

HIV-1 infection increases metabolic activation in CD4+ T cells

A hallmark of HIV-1 infection is the inexorable decline of CD4+ T cells in the absence of cART, that is primarily determined by immune activation, high cell turnover and apoptosis. The concept of HIV-induced metabolic activation of CD4+ T cells have not been recognized before. Metabolic activation in this context may be defined as an increase in biochemical activity to promote glucose uptake and metabolism in CD4+ T cells to provide energy in the form of ATP for cellular functions. There is limited data accounting for a direct effect of HIV-1 infection on T cell metabolism related to their survival, differentiation and functions. However, earlier research of other viruses studied in non-human systems illustrated that murine sarcoma and Rous sarcoma virus-infected cells take up more glucose than uninfected cells [54-57]. More recently, Glut1 expression and glucose uptake were shown to be elevated in polyoma virus-infected mouse fibroblasts [58] and in humans, fibroblast human cytomegalovirus (HCMV) infection induces a dramatic increase in glycolysis [59, 60].

The first evidence related to the impact of HIV-1 on glucose uptake and metabolism in T cells came from a study by Sorbara and colleagues who showed an increase in glucose uptake in cultures of human T cell line (H9) infected with HIV-1. This was associated with moderate increases in the cell surface expression of Glut1 and Glut3 [61]. Their findings were supported by a more recent publication by Hollenbaugh and co-workers that showed significant increase in glucose uptake in primary CD4+ T cells infected with HIV-1 in culture and a concomitant increase in the levels of key glycolytic metabolites such as hexose-P, fructose 1,6-bisphosphate and glyceraldehyde-3P [36]. Alteration in glucose transporter expression and changes in metabolite profiles are likely to modify the intracellular metabolic environment of CD4+ T cells, thereby conferring an adaptive advantage that enables HIV-1 to change its metabolic profile to favour infection and replication. Interestingly, researchers

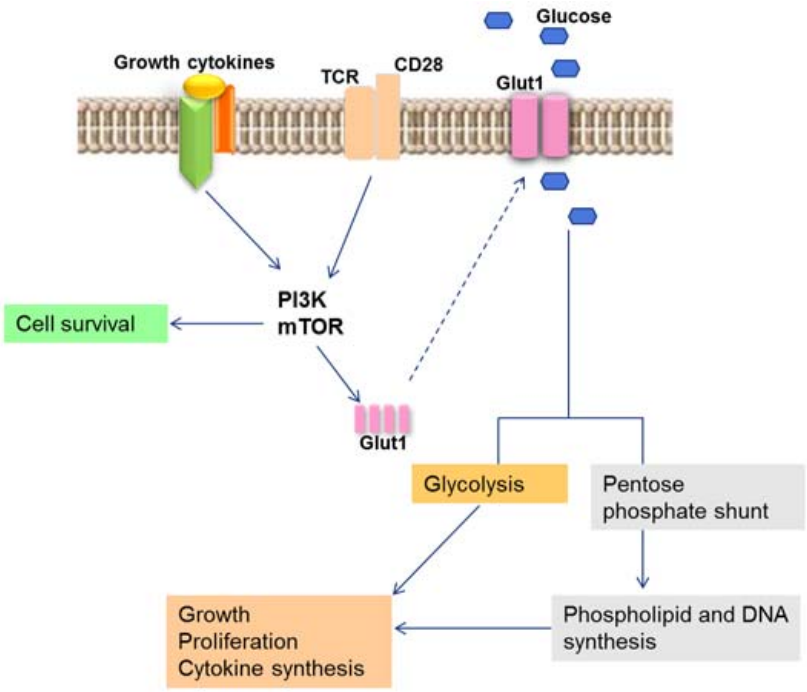

Figure 2. **Growth cytokine stimulation and engagement of the TCR complex activates the phosphoinositide 3-kinase (PI3K) and Mammalian Target of Rapamycin (mTOR) pathways**. Optimum activation of the PI3K and mTOR pathways upregulate genes associated with cell survival and promotes Glut1 translocation from the cytoplasm to the cell surface membrane. In activated T cells, the major pathways for the cellular fate of glucose are glycolysis to generate ATP and the pentose phosphate shunt to synthesize intermediates for phospholipids and DNA, required for membrane synthesis and cell division. TCR; T cell receptor, PI3K; phosphoinositide 3-kinase, mTOR; Mammalian Target of Rapamycin, Glut1; Glucose transporter-1.

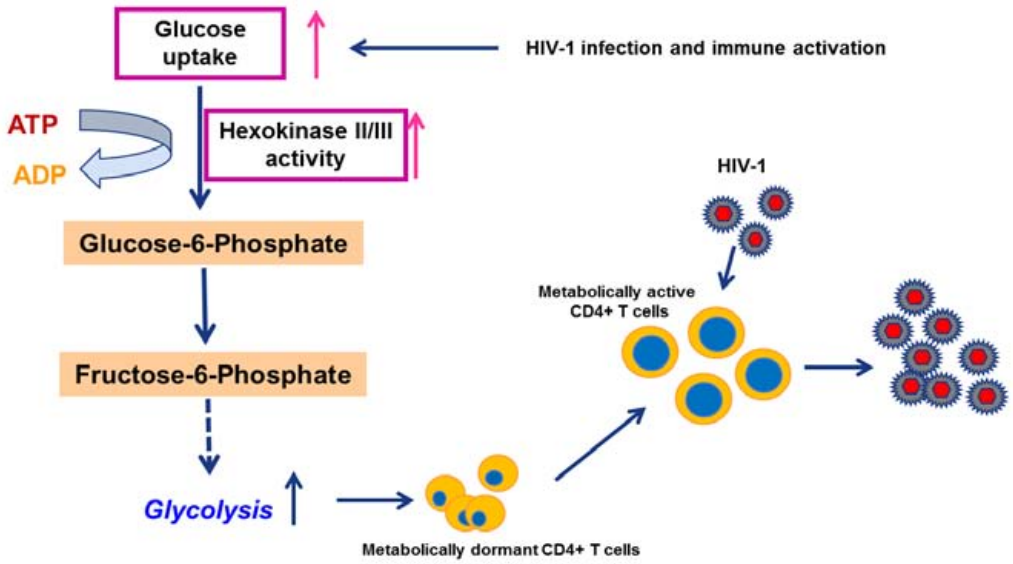

Figure 3. **Proposed mechanism by which HIV-1 may induce hypermetabolic responses to perpetuate infection of CD4+ T cells**. A combination of viral and environmental factors during HIV-1 infection induces glucose uptake and activation of glycolysis providing a favourable metabolic profile for HIV-1 infection and replication.

studying the Human T cell Leukemia Virus demonstrated that TCR stimulation of T cells induces Glut1 cell surface expression with a corresponding increase in the binding of HTLV-1 and HTLV-2 envelope glycoproteins. Further, ectopic expression of Glut1, but not Glut3, on 293 T cell lines induced the binding capacity of these envelope glycoproteins concluding that Glut1 is the primary binding receptor for HTLV-1 and HTLV-2 [62, 63]. Since HIV-1, HTLV-1 and HTLV-2 are retroviruses, it is possible that the cell surface expression of Glut1 on activated CD4+ T cell might be a requirement for HIV-1 binding and entry. Taken together, we summarize the likely scenario by which HIV-1 infection may increase CD4+ T cell metabolic activity to facilitate and perpetuate further infection of CD4+ T cells (Figure 3). The increased metabolic activity of CD4+ T cells in response to HIV-1 infection is likely to be in part due to the activation of the PI3K-Akt pathway by HIV-1 Tat protein [64].

During HIV-1 infection, even in the presence of cART, prolonged metabolic activation or "hypermetabolism" driven by continuous antigenic stimulation and inflammation may contribute to T cell metabolic exhaustion and the subsequent loss of CD4+ T cells. This raises the possibility of whether therapeutic manipulation of metabolic pathways such as PI3K and mTOR could normalize metabolism in CD4+ T cells and reduce the progressive CD4+ T cell depletion during HIV-1 infection. In agreement with this, it has been shown that the potent inhibitor of mTOR, rapamycin, possesses *in vivo* antiviral properties against CCR5 strains of HIV-1. Additionally, a recent prospective trial of liver-transplanted HIV-infected patients receiving rapamycin monotherapy demonstrated significant improvement in HIV-1 control [65, 66].

Metabolic profile of monocytes and macrophages during HIV-1 infection

There is a paucity of data relating to the metabolic profile of cells of macrophage lineage, especially during HIV-1 infection. Monocytes are terminally differentiated cells and upon activation, their cell surface expression of Glut1, Glut3 and Glut4 are increased. Only Glut3 and Glut4 are responsive to insulin in either the resting or activated states of monocytes. One of the most significant events in the formation of atherosclerotic lesions involves the attachment and transendothelial migration of activated monocytes, their subsequent differentiation into macrophages and transformation into lipid-loaded foam cells [67].

THP-1 monocyte differentiation into macrophages and foam cells is associated with increased surface expression of the glucose transporters Glut1, Glut3 and Glut5 [42]. Unlike T cells which increase their glucose uptake for growth and proliferation, activated macrophages increase nutrient uptake to enhance their immune functions of phagocytosis and secretory activity, such as reactive oxygen species and transendothelial migration as part of immune surveillance. These functions are impacted by HIV-1 infection [68, 69] and contribute to the development of those opportunistic infections where macrophage function is important for their control (e.g. *Mycobacterium tuberculosis* infection, *Mycobacterium avium* complex, toxoplasmosis and cryptococcal disease) and possibly increasing the risk of non-AIDS morbidities including cardiovascular disease.

A subset of monocytes can be infected with HIV-1 [70] whilst mature, differentiated macrophages are more susceptible to infection [71]. It is not established whether HIV-1 infection promotes changes in glucose metabolic profile in primary monocytes and whether this accelerates their differentiation into macrophages. However, contrary to CD4+ T cells, the HIV-1infected monocytic cell line (U1) has significantly reduced glucose uptake and glycolysis compared to the uninfected parent line, but increased metabolism via the TCA cycle [36].

Effects of the HIV-1 inflammatory environment and common gamma chain cytokines on glucose uptake in T cells

The chronic inflammation associated with HIV-1 infection is similar to that observed in obese individuals with insulin resistance and type 2 diabetes (T2D), metabolic conditions characterized by poor glucose uptake by tissues such as the muscle. This inflammatory state could similarly subject T cells to conditions which may impede efficient glucose uptake and metabolism. Homeostasis of peripheral T cells is accomplished

through a combination of programmed cell death, normal cell turnover and cellular survival signals [72]. Cytokines such as the common gamma chain cytokines (IL-2, IL-7, IL-15 and IL-21) are important for CD4 and CD8+ T cell signalling, survival and function, and they act via a common γ-chain receptor to promote glucose uptake [52]. During HIV-1 infection there is an imbalance in the levels of the common gamma chain cytokines. These cytokines have gained considerable interest due to their ability to enhance glucose uptake [52] and encourage T cell survival [73]. However, in recent clinical trials, subcutaneous injections of recombinant IL-2 and IL-7 have had unfavourable immunological effects with transient increases in viral replication reported. These disappointing results are likely due to the severe immunodeficiency at baseline for many of the study participants [74-77] or perhaps an inherited non-responsiveness to these cytokines. A better understanding of the biochemical effects of the common gamma chain family of cytokines might enable better predictions of their success in the clinic.

Adipose tissue, adipokines and HIV-1 pathogenesis

Adipose tissue biology and HIV-1 infection

HIV-1/cART-associated lipodystrophy syndrome is a disorder resulting from the redistribution of adipose tissue and characterized by atrophy of subcutaneous adipose tissue (lipoatrophy), with visceral adipose tissue hypertrophy and accumulation of dorso-cervical fat (phenotypically described as 'buffalo hump') [78, 79]. The pathophysiology of this syndrome is multifactorial but the key metabolic disturbances include dysregulated adipocyte differentiation, high adipocyte lipolysis, and adipocyte apoptosis [80]. These changes in adipose tissue biology expand to involve systemic metabolism through alterations in endocrine functions of adipose tissue via adipokine release (such as adiponectin, leptin, resistin, visfatin and chemerin), enhanced production of pro-inflammatory cytokines and excessive free fatty-acid release due to lipolysis [81, 82]. Many HIV-1 protease inhibitors elicit these modifications in adipose tissue [83, 84]. However, as discussed below HIV-1 encoded proteins may also contribute directly to the development of HIV-1/cART-associated lipodystrophy syndrome through their effects on lipid homeostasis in adipocytes and by promoting a local inflammatory environment in adipose tissue. The adipokines are a critical link between the adipose tissue, peripheral tissue metabolism and immune responses. In this context, adiponectin has received the most attention due to its dual metabolic and immunoregulatory properties.

Role of adiponectin and adiponectin receptors on leucocyte functions

Adiponectin is the most abundant serum adipokine and is paradoxically reduced in subjects who are obese or those exhibiting features of the metabolic syndrome such as insulin resistance and T2D. Circulating adiponectin exists in high, medium and low molecular weight forms, of which the high molecular weight form is considered the most physiologically important [16]. Adiponectin improves insulin sensitivity, promotes vascular health, and increases cell survival by regulating glucose and lipid metabolism through AMPK and peroxisome proliferator activated receptor alpha (PPAR-α) ligand activity [85]. These findings concur with a potential therapeutic role for adiponectin in the treatment of T2D, cardiovascular diseases, cancers and other metabolic and inflammatory conditions. The underlying mechanism for adiponectin activity is likely to include the activation of adenosine monophosphate-activated protein kinase (AMPK) downstream of its two receptors (AdipoR1 and AdipoR2).

HIV-1-infected patients on cART often exhibit hypoadiponectinemia which is associated with insulin resistance, central fat and lipoatrophy [86, 87]. In transgenic mice expressing an HIV-1 construct, adiponectin gene expression was repressed in WAT in concert with reduced expression of PPAR-γ, a master regulator of adipogenesis. In overweight HIV-negative subjects, lifestyle modification increases serum concentrations of adiponectin and improves their lipid profiles [88, 89]. Similar lifestyle modification and chemotherapy have been shown to ameliorate hypoadiponectinemia in patients with HIV-1/cART-associated dyslipidaemia [90-92] providing an opportunity for such interventions to improve or restore lipodystrophy in patients on cART.

The direct impact of hypoadiponectinemia on leukocyte functions in the setting of HIV-1 infection is uncharted. Nonetheless, adiponectin receptors AdipoR1 and AdipoR2 are expressed on B lymphocytes, monocytes, NK cells, CD4 and CD8+ T cells [16, 93, 94] and in the setting of other chronic viral diseases, such as HCV infection, high molecular weight adiponectin appears to have a positive effect on the T cellular immune responses [16]. A direct effect of adiponectin on the functions of monocytes and macrophages has been established. Low molecular weight but not high molecular weight adiponectin reduces LPS-mediated IL-6 release and stimulates IL-10 secretion in THP-1 human monocytic cells [95]. Hence, strategies that promote high circulating levels of adiponectin could potentially alleviate chronic inflammation induced in part by low level endotoxemia in HIV-1-infected individuals. Adiponectin might also attenuate inflammation by polarizing monocyte-derived macrophages from an inflammatory M1 to a pro-inflammatory M2 phenotype [96, 97].

cART, adipose tissue and metabolic dysfunction during HIV-1 infection

cART consists of a combination of antiretroviral drugs that inhibit HIV-1 replication. Although cART accounts for a significant reduction in AIDS-related mortality, metabolic disorders such as subcutaneous adipose tissue wasting, dyslipidemia and Type 2 diabetes (T2D) have been associated with some cART regimens and contribute to the risk of cardiovascular disease in this population. Most studies of glucose and lipid metabolic abnormalities have focussed on cART-experienced rather than treatment-naïve subjects. Even though traditional risk factors such as body mass index and smoking are often confounders in studies, antiretroviral medications appear to play a causative or permissive role in the pathogenesis of insulin resistance, hyperglycaemia and the risk of T2D in HIV-1-infected patients [98, 99]. A direct impact of HIV-1 on the development of insulin resistance and T2D is less well defined. Nonetheless, it is acknowledged that increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α during HIV-1 infection are key players in the pathogenesis of insulin resistance and T2D [100, 101].

In one of the largest studies conducted to date, the prevalence and incidence of T2D was evaluated in the Multicenter AIDS Cohort Study involving 710 HIV-1 seronegative and 411 HIV-1-infected patients undergoing cART [102]. Their analysis revealed that 14% of those on a protease inhibitor-containing regimen had T2D, compared to 5% of seronegative men. Of the antiretroviral drugs investigated, protease inhibitors have the greatest impact on lipid and glucose metabolic changes and regulation. Several studies have demonstrated that ritonavir induces insulin resistance in patients with long term exposure to cART due to altered lipid metabolism and adipokine profiles [103]. Some third generation protease inhibitors such as darunavir and atazanavir show more favourable lipid and glucose profiles in healthy subjects in a short term study [104]. By contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the least impact on lipid distribution, dyslipidaemia or glucose metabolism. In a cross-sectional observational study involving 101 patients, the effect of three regimens that include an NNRTI (nevirapine) backbone and two NRTIs were evaluated for effects on lipodystrophy for at least two years [105]. In this study, no differences in lipoatrophy, central fat accumulation, dyslipidaemia or glucose metabolism were observed among patients receiving any of the three different nevirapine plus nucleoside backbone-containing regimens.

Mechanisms of induction of insulin resistance by antiretroviral drugs

For many years, the interpretation of insulin resistance and glucose homeostasis was sculptured around a “glucocentric” axis. Now perturbation of lipid homeostasis has emerged as a key player in dysregulated glucose metabolism. Elevated circulating levels of free fatty acids are observed prior to the onset of glucose intolerance and this has caused a major paradigm shift on how we understand the pathogenesis and clinical complications of glucose metabolism and T2D [106].

Free fatty acids such as palmitic acid induce hepatic insulin resistance and blunt the ability of the liver to regulate glucose production [107]. Lipid homeostasis is tightly controlled in the adipose tissue and liver by several genes that act co-ordinately to promote equilibrium between

lipid biosynthesis and oxidation. It is not always possible to distinguish the effects of each class of drug in a cART regimen in data from clinical trials. It is not ethical to use monotherapy, therefore *in vitro* experiments offer the best means to dissect the degree and underlying mechanism of metabolic disturbances associated with cART. Minami and co-workers evaluated the effect of four classes of antiretroviral drugs on lipid accumulation in an adipocyte cell line, 3T3-L1. In this study, all the HIV-1 protease inhibitors, NNRTIs and NRTIs but not the integrase inhibitor raltegravir, caused a decrease in lipid accumulation in mature and immature 3T3-L1 cells. Most of the drugs evaluated except raltegravir caused significant decrease in mRNA expression of the central lipogenic transcription factors C/EBP-α, and SREBP-1C in pre-differentiated 3T3-L1 cells. Overall, the protease inhibitors showed a stronger inhibition of these central lipogenic transcription factors which is considered a key mechanism for cART-associated lipoatrophy [108]. Protease inhibitors such as nelfinavir also impair insulin signalling pathways by reducing insulin-induced phosphorylation of insulin-receptor substrate-1 and Akt activation, resulting in reduced Glut4 translocation and diminished glucose uptake in adipocytes [98]. The metabolic effects of antiretroviral drugs on immune cells are less studied but work by Yilmaz and colleagues has shown that, in peripheral blood mononuclear cells of HIV-seronegative healthy individuals, ritonavir significantly reduced the expression of genes associated with the prevention of atherosclerosis and inflammation [109].

The etiology of HIV-1/cART-associated lipodystrophy is likely to be multifactorial in nature. As discussed in the next section, HIV-1 may directly dysregulate fatty acid metabolism and also instigate the production of proinflammatory cytokines.

Direct effects of HIV-metabolism in adipocytes

The white adipocytes express CD4, CCR5, and CXCR4 receptors allowing them to potentially support low levels of HIV-1 replication [110]. In insulin stimulated adipocytes, HIV-1 Nef inhibits Akt phosphorylation and activation, disrupts actin-remodeling and attenuates Glut4 translocation and fusion with the plasma membrane. This results in a Nef-dependent inhibition of glucose uptake in adipocytes, implicating Nef in the development of HIV-1-associated insulin resistance and T2D [64]. From a different perspective, since the adipose tissue also contains CD4+ T cells and macrophages, it is likely that HIV-1-infected cells within these reservoirs could secrete pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α which are known to inhibit adiponectin expression, impair insulin sensitivity and perpetuate a local inflammatory response. It would be of interest to know whether low levels of viral replication continue to occur in the adipose tissue compartments during HIV-1 cART and if this contributes to the persistent chronic inflammation in HIV-1 treatment experienced individuals.

CONCLUDING REMARKS

Increasing attention is being paid to understanding the immunoregulatory functions of adipose tissue and the impact on immune responses to viral infection and cancers. It is also becoming clearer that the function and differentiation of leukocytes are determined by their intrinsic metabolic profiles that must continuously change to adapt to their environment. The data reviewed here suggest that increased cell surface expression of the glucose transporter, Glut1 and the subsequent increase in glucose uptake and metabolism through glycolysis is a major metabolic response by T cells during the immune responses to viral infections, a process partially mediated by hyper-activation of the PI3K-Akt-mTOR cell survival pathway. The changing metabolic profiles of CD4+ T cells on HIV-1 exposure might allow them to become more susceptible to HIV-1 infection and apoptosis. Preclinical evidence suggests that inhibitors of the PI3K-Akt-mTOR axis such as rapamycin could provide a novel therapeutic strategy to preserve the CD4+ T cell population, attenuate the natural course of HIV-1 infection and reduce the risk of acquiring HIV-associated co-morbidities. Targeting components of the glucose metabolic machinery such as Glut1 and hexokinase II in T cells may be a potential strategy to normalize their metabolic activity and help to promote immune recovery. Another attractive concept proposed is the use of clinically available inhibitors of the PI3K-Akt to hyper-sensitize long lived HIV-1-infected macrophage to cellular stress as a strategy to deplete these viral reservoirs.

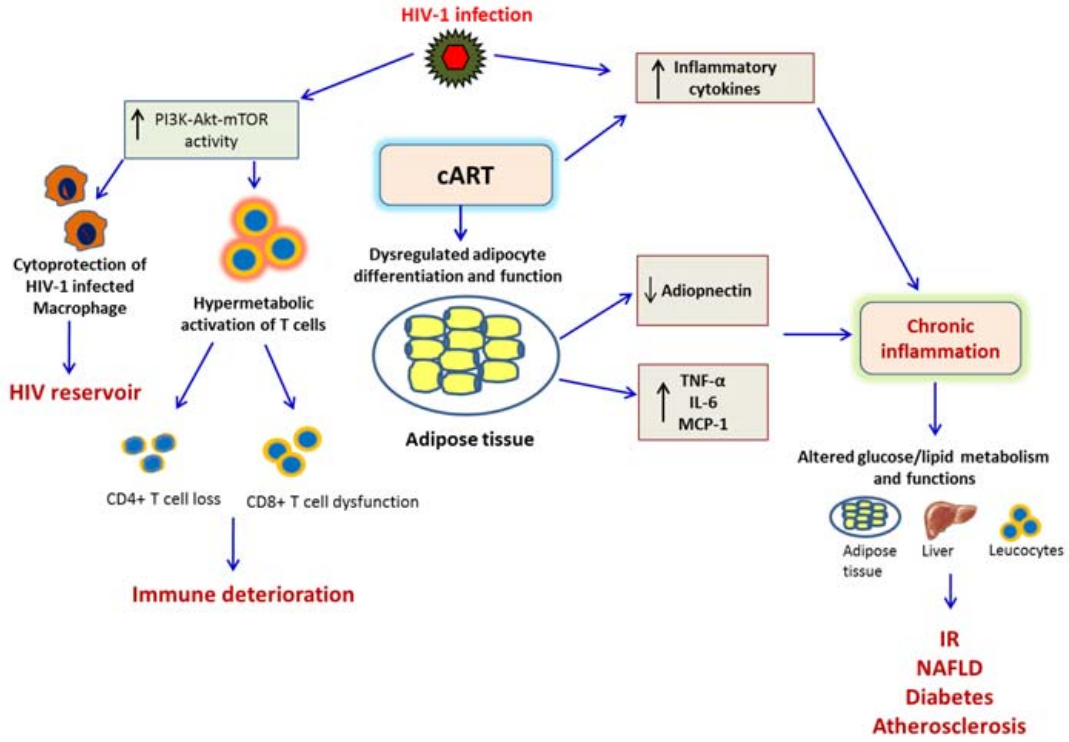

Figure 4. Involvement of HIV-1 infection and cART in metabolic dysfunction in infected subjects. During HIV-1 infection defects in the PI3K-Akt-mTOR pathway is involved in the cytoprotection of HIV-1 infected macrophage and hypermetabolic activation of T cells and immune deterioration. HIV-1 and cART-induced metabolic and inflammatory responses induce chronic inflammation which predisposes individuals to insulin resistance (IR), non-alcoholic fatty liver disease (NAFLD), diabetes and atherosclerosis.

Some cART regimens are strongly associated with insulin resistance, diabetes, dyslipidemia and hypertension. This heightens the risk of serious long term co-morbidities in HIV-1 infected individuals. A central mode of action of many of the HIV-1 antiviral drugs is dysregulation of the white adipose tissue. A greater appreciation and understanding of the biology of the adipose tissue in the context of HIV-1 infection will help to guide the development of lipid-friendlier antiretroviral drugs. Our current understanding of the interactions between the metabolic consequences of direct HIV-1 infection, and cART-induced metabolic disturbances in HIV-1 positive patients are summarized in Figure 4.

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REFERENCES

1. Michalek, R. D. and Rathmell, J. C. 2010, Immunol. Rev., 236, 190.
2. Fox, C. J., Hammerman, P. S., and Thompson, C. B. 2005, Nat. Rev. Immunol., 5, 844.
3. Zheng, Y., Delgoffe, G. M., Meyer, C. F., Chan, W., and Powell, J. D. 2009, J. Immunol., 183, 6095.
4. Parvaiz, F., Manzoor, S., Tariq, H., Javed, F., Fatima, K., and Qadri, I. 2011, Virol. J., 8, 474.

5. Bassendine, M. F., Sheridan, D. A., Felmlee, D. J., Bridge, S. H., Toms, G. L., and Neely, R. D. 2011, J. Hepatol., 55, 1428.
6. Miyoshi, H., Moriya, K., Tsutsumi, T., Shinzawa, S., Fujie, H., Shintani, Y., Fujinaga, H., Goto, K., Todoroki, T., Suzuki, T., Miyamura, T., Matsuura, Y., Yotsuyanagi, H., and Koike, K. 2011, J. Hepatol., 54, 432.
7. Shimizu, Y., Hishiki, T., Sugiyama, K., Ogawa, K., Funami, K., Kato, A., Ohsaki, Y., Fujimoto, T., Takaku, H., and Shimotohno, K. 2010, Virology, 407, 152.
8. Negro, F. 2010, Gut, 59, 1279.
9. Grasso, A., Malfatti, F., De Leo, P., Martines, H., Fabris, P., Toscanini, F., Anselmo, M., and Menardo, G. 2009, J. Hepatol., 51, 984.
10. Cua, I. H., Hui, J. M., Kench, J. G., and George, J. 2008, Hepatology (Baltimore, Md.), 48, 723.
11. Reddy, K. R., Shiffman, M. L., Rodriguez-Torres, M., Cheinquer, H., Abdurakhmanov, D., Bakulin, I., Morozov, V., Silva, G. F., Geyvandova, N., Stanciu, C., Rabbia, M., Mckenna, M., Thommes, J. A., and Harrison, S. A. 2010, Gastroenterology, 139, 1972.
12. Tarantino, G., Conca, P., Sorrentino, P., and Ariello, M. 2006, J. Gastroenterol. Hepatol., 21, 1266.
13. Walsh, M. J., Jonsson, J. R., Richardson, M. M., Lipka, G. M., Purdie, D. M., Clouston, A. D., and Powell, E. E. 2006, Gut, 55, 529.
14. Bressler, B. L., Guindi, M., Tomlinson, G., and Heathcote, J. 2003, Hepatology (Baltimore, Md.), 38, 639.
15. Elgouhari, H. M., Zein, C. O., Hanouneh, I., Feldstein, A. E., and Zein, N. N. 2009, Dig. Dis. Sci., 54, 2699.
16. Palmer, C., Hampartzoumian, T., Lloyd, A., and Zekry, A. 2008, Hepatology (Baltimore, Md.), 48, 374.
17. Rhoads, M. P., Lanigan, J., Smith, C. J., and Lyall, E. G. 2011, J. Acquir. Immune Defic. Syndr., 57, 404.
18. Padmapriyadarsini, C., Ramesh Kumar, S., Terrin, N., Narendran, G., Menon, P. A., Ramachandran, G., Subramanyan, S., Venkatesan, P., Wanke, C., and Swaminathan, S. 2011, Clinical infectious diseases : An official publication of the Infectious Diseases Society of America, 52, 540.
19. Dimock, D., Thomas, V., Cushing, A., Purdy, J. B., Worrell, C., Kopp, J. B., Hazra, R., and Hadigan, C. 2011, Metabolism, 60, 874.
20. Van Vonderen, M. G., Blumer, R. M., Hassink, E. A., Sutinen, J., Ackermans, M. T., Van Agtmael, M. A., Yki-Jarvinen, H., Danner, S. A., Serlie, M. J., Sauerwein, H. P., and Reiss, P. 2010, Journal of Acquired Immune Deficiency Syndromes (1999), 53, 186.
21. Sievers, M., Walker, U. A., Sevastianova, K., Setzer, B., Wagsater, D., Eriksson, P., Yki-Jarvinen, H., and Sutinen, J. 2009, The Journal of Infectious Diseases, 200, 252.
22. Stanley, T. L., Joy, T., Hadigan, C. M., Liebau, J. G., Makimura, H., Chen, C. Y., Thomas, B. J., Weise, S. B., Robbins, G. K., and Grinspoon, S. K. 2009, AIDS (London, England), 23, 1349.
23. Blanco, F., San Roman, J., Vispo, E., Lopez, M., Salto, A., Abad, V., and Soriano, V. 2010, AIDS Rev., 12, 231.
24. Noor, M. A. 2007, Curr. HIV/AIDS Rep., 4, 126.
25. Van Wijk, J. P. and Cabezas, M. C. 2012, Int. J. Vasc. Med., 2012, 201027.
26. Powell, J. D., Pollizzi, K. N., Heikamp, E. B., and Horton, M. R. 2012, Annual Review of Immunology, 30, 39.
27. Chawla, A., Nguyen, K. D., and Goh, Y. P. 2011, Nature reviews Immunology, 11, 738.
28. Ouchi, N., Parker, J. L., Lugus, J. J., and Walsh, K. 2011, Nature reviews. Immunology, 11, 85.
29. Finlay, D. and Cantrell, D. A. 2011, Nature reviews Immunology, 11, 109.
30. Mathis, D. and Shoelson, S. E. 2011, Nature reviews Immunology, 11, 81.
31. Deiuliis, J., Shah, Z., Shah, N., Needleman, B., Mikami, D., Narula, V., Perry, K., Hazey, J., Kampfrath, T., Kollengode, M., Sun, Q., Satoskar, A. R., Lumeng, C., Moffatt-Bruce, S., and Rajagopalan, S. 2011, PLoS One, 6, e16376.
32. Nishimura, S., Manabe, I., Nagasaki, M., Eto, K., Yamashita, H., Ohsugi, M., Otsu, M., Hara, K., Ueki, K., Sugiura, S., Yoshimura, K., Kadowaki, T., and Nagai, R. 2009, Nat. Med., 15, 914.

33. Xue, B., Sukumaran, S., Nie, J., Jusko, W. J., Dubois, D. C., and Almon, R. R. 2011, PLoS One, 6, e17386.
34. Deeks, S. G. 2009, Top HIV Med., 17, 118.
35. Crowe, S. M., Westhorpe, C. L., Mukhamedova, N., Jaworowski, A., Sviridov, D., and Bukrinsky, M. 2010, J. Leukoc. Biol., 87, 589.
36. Hollenbaugh, J. A., Munger, J., and Kim, B. 2011, Virology, 415, 153.
37. Kim, Y., Hollenbaugh, J. A., Kim, D.-H., and Kim, B. 2011, PLoS One, 6, e21781.
38. Jacobs, S. R., Herman, C. E., Maciver, N. J., Wofford, J. A., Wieman, H. L., Hammen, J. J., and Rathmell, J. C. 2008, J. Immunol., 180, 4476.
39. Cham, C. M. and Gajewski, T. F. 2005, Journal of Immunology (Baltimore, Md. : 1950), 174, 4670.
40. Alves, N. L., Derks, I. A., Berk, E., Spijker, R., Van Lier, R. A., and Eldering, E. 2006, Immunity, 24, 703.
41. Warburg, O. 1956, Science (New York, N.Y.), 123, 309.
42. Fu, Y., Maianu, L., Melbert, B. R., and Garvey, W. T. 2004, Blood cells, Molecules & Diseases, 32, 182.
43. Maratou, E., Dimitriadis, G., Kollias, A., Boutati, E., Lambadiari, V., Mitrou, P., and Raptis, S. A. 2007, Eur. J. Clin. Invest., 37, 282.
44. Barata, J., Boussiotis, V., Yunes, J., Ferrando, A., Moreau, L., Veiga, J., Sallan, S., Look, A., Nadler, L., and Cardoso, A. 2004, Blood, 103, 1891
45. Delgoffe, G. M. and Powell, J. D. 2009, Immunology, 127, 459.
46. Wieman, H. L., Wofford, J. A., and Rathmell, J. C. 2007, Mol. Biol. Cell, 18, 1437.
47. Frauwirth, K. A. and Thompson, C. B. 2004, J. Immunol., 172, 4661.
48. Pearce, E. L. 2010, Current Opinion in Immunology, 22, 314.
49. Marko, A. J., Miller, R. A., Kelman, A., and Frauwirth, K. A., PLoS One, 5, e15425.
50. Wofford, J. A., Wieman, H. L., Jacobs, S. R., Zhao, Y., and Rathmell, J. C. 2008, Blood, 111, 2101.
51. Tamas, P., Hawley, S. A., Clarke, R. G., Mustard, K. J., Green, K., Hardie, D. G., and Cantrell, D. A. 2006, The Journal of Experimental Medicine, 203, 1665.
52. Chehtane, M. and Khaled, A. R. 2010, American Journal of Physiology Cell Physiology, 298, C1560.
53. Marko, A. J., Miller, R. A., Kelman, A., and Frauwirth, K. A. 2010, PLoS One, 5, e15425.
54. Hatanaka, M. and Hanafusa, H. 1970, Virology, 41, 647.
55. Isselbacher, K. J. 1972, Proceedings of the National Academy of Sciences of the United States of America, 69, 585.
56. Bader, J. P., Brown, N. R., and Ray, D. A. 1981, Cancer Res., 41, 1702.
57. Lang, D. R. and Weber, M. J. 1978, J. Cell Physiol., 94, 315.
58. Young, A. T., Dahl, J., Hausdorff, S. F., Bauer, P. H., Birnbaum, M. J., and Benjamin, T. L. 1995, Proceedings of the National Academy of Sciences of the United States of America, 92, 11613.
59. Yu, Y., Clippinger, A. J., and Alwine, J. C. 2011, Trends Microbiol., 19, 360.
60. Yu, Y., Clippinger, A. J., Pierciey, Jr. F. J., and Alwine, J. C. 2011, Chapter 3 - Viruses and Metabolism: Alterations of Glucose and Glutamine Metabolism Mediated by Human Cytomegalovirus, Karl Maramorosch, A. J. S. and Frederick, A. M. (Eds.), Adv. Virus Res. Academic Press, pp 49.
61. Sorbara, L. R., Maldarelli, F., Chamoun, G., Schilling, B., Chokekijcahi, S., Staudt, L., Mitsuya, H., Simpson, I. A., and Zeichner, S. L. 1996, J. Virol., 70, 7275.
62. Kinet, S., Swainson, L., Lavanya, M., Mongellaz, C., Montel-Hagen, A., Craveiro, M., Manel, N., Battini, J.-L., Sitbon, M., and Taylor, N. 2007, Retrovirology, 4, 31.
63. Manel, N., Kim, F. J., Kinet, S., Taylor, N., Sitbon, M., and Battini, J. L. 2003, Cell, 115, 449.
64. Cheney, L., Hou, J. C., Morrison, S., Pessin, J., and Steigbigel, R. T. 2011, Journal of Infectious Diseases, 203, 1824.
65. Nicoletti, F., Fagone, P., Meroni, P., Mccubrey, J., and Bendtzen, K. 2011, Drug Discovery Today, 16, 715.

66. Di Benedetto, F., Di Sandro, S., De Ruvo, N., Montalti, R., Ballarin, R., Guerrini, G. P., Spaggiari, M., Guaraldi, G., and Gerunda, G. 2010, Transplantation, 89, 733.
67. Fu, Y., Luo, N., and Lopes-Virella, M. F. 2002, Atherosclerosis, 160, 11.
68. Kedzierska, K., Ellery, P., Mak, J., Lewin, S. R., Crowe, S. M., and Jaworowski, A. 2002, Journal of Immunology (Baltimore, Md. : 1950), 168, 2895.
69. Westhorpe, C. L., Zhou, J., Webster, N. L., Kalionis, B., Lewin, S. R., Jaworowski, A., Muller, W. A., and Crowe, S. M. 2009, J. Leukoc. Biol., 85, 1027.
70. Ellery, P. J., Tippett, E., Chiu, Y. L., Paukovics, G., Cameron, P. U., Solomon, A., Lewin, S. R., Gorry, P. R., Jaworowski, A., Greene, W. C., Sonza, S., and Crowe, S. M. 2007, Journal of Immunology (Baltimore, Md. : 1950), 178, 6581.
71. Sonza, S., Maerz, A., Deacon, N., Meanger, J., Mills, J., and Crowe, S. 1996, J. Virol., 70, 3863.
72. Kitchen, C. M., Yeghiazarian, L., Hoh, R., Mccune, J. M., Sinclair, E., Martin, J. N., and Deeks, S. G. 2011, PLoS One, 6, e21190.
73. Kim, H.-R., Hwang, K.-A., and Kang, I. 2007, J. Immunol., 179, 6734.
74. Levy, Y., Lacabaratz, C., Weiss, L., Viard, J. P., Goujard, C., Lelievre, J. D., Boue, F., Molina, J. M., Rouzioux, C., Avettand-Fenoel, V., Croughs, T., Beq, S., Thiebaut, R., Chene, G., Morre, M., and Delfraissy, J. F. 2009, The Journal of Clinical Investigation, 119, 997.
75. Fontas, E., Kousignian, I., Pradier, C., Poizot-Martin, I., Durier, C., Weiss, L., Levy, Y., and Costagliola, D. 2010, The Journal of Antimicrobial Chemotherapy, 65, 2215.
76. Weiss, L., Letimier, F. A., Carriere, M., Maiella, S., Donkova-Petrini, V., Targat, B., Benecke, A., Rogge, L., and Levy, Y. 2010, Proceedings of the National Academy of Sciences of the United States of America, 107, 10632.
77. Abrams, D., Levy, Y., Losso, M. H., Babiker, A., Collins, G., Cooper, D. A., Darbyshire, J., Emery, S., Fox, L., Gordin, F., Lane, H. C., Lundgren, J. D., Mitsuyasu, R., Neaton, J. D., Phillips, A., Routy, J. P., Tambussi, G., and Wentworth, D. 2009, The New England Journal of Medicine, 361, 1548.
78. Guallar, J. P., Gallego-Escuredo, J. M., Domingo, J. C., Alegre, M., Fontdevila, J., Martinez, E., Hammond, E. L., Domingo, P., Giralt, M., and Villarroya, F. 2008, AIDS (London, England), 22, 575.
79. Grunfeld, C., Rimland, D., Gibert, C. L., Powderly, W. G., Sidney, S., Shlipak, M. G., Bacchetti, P., Scherzer, R., Haffner, S., and Heymsfield, S. B. 2007, Journal of Acquired Immune Deficiency Syndromes (1999), 46, 283.
80. Lichtenstein, K., Balasubramanyam, A., Sekhar, R., and Freedland, E. 2007, AIDS Res. Ther., 4, 14.
81. Carr, A., Ritzhaupt, A., Zhang, W., Zajdenverg, R., Workman, C., Gatell, J. M., Cahn, P., and Chaves, R. 2008, AIDS (London, England), 22, 2313.
82. Spagnuolo, M. I., Bruzzese, E., Vallone, G. F., Fasano, N., De Marco, G., Officioso, A., Valerio, G., Volpicelli, M., Iorio, R., Franzese, A., and Guarino, A. 2008, J. Endocrinol. Invest., 31, 592.
83. Lagathu, C., Eustace, B., Prot, M., Frantz, D., Gu, Y., Bastard, J. P., Maachi, M., Azoulay, S., Briggs, M., Caron, M., and Capeau, J. 2007, Antivir. Ther., 12, 489.
84. Leroyer, S., Vatier, C., Kadiri, S., Quette, J., Chapron, C., Capeau, J., and Antoine, B. 2011, J. Lipid Res., 52, 207.
85. Kadowaki, T. and Yamauchi, T. 2011, Cell Metabolism, 13, 123.
86. Vigano, A., Zuccotti, G. V., Cerini, C., Stucchi, S., Puzzovio, M., Giacomet, V., and Mora, S. 2012, Current HIV Research, 9, 321.
87. Deloumeaux, J., Maachi, M., Sow-Goerger, M. T., Lamaury, I., Velayoudom, F. L., Cheret, A., Batard, M. L., Muller, P., Bastard, J. P., Chene, G., Capeau, J., and Foucan, L. 2011, Diabetes Metab., 37, 98.

88. Rynders, C., Weltman, A., Delgiorno, C., Balagopal, P., Damaso, L., Killen, K., and Mauras, N. 2012, Med. Sci. Sports Exerc., 44, 786.
89. Koncsos, P., Seres, I., Harangi, M., Pall, D., Jozsa, L., Bajnok, L., Nagy, E. V., and Paragh, G. 2011, J. Am. Coll. Nutr., 30, 333.
90. Balasubramanyam, A., Coraza, I., Smith, E. O., Scott, L. W., Patel, P., Iyer, D., Taylor, A. A., Giordano, T. P., Sekhar, R. V., Clark, P., Cuevas-Sanchez, E., Kamble, S., Ballantyne, C. M., and Pownall, H. J. 2011, The Journal of Clinical Endocrinology and Metabolism, 96, 2236.
91. Yarasheski, K. E., Cade, W. T., Overton, E. T., Mondy, K. E., Hubert, S., Laciny, E., Bopp, C., Lassa-Claxton, S., and Reeds, D. N. 2011, Am. J. Physiol. Endocrinol. Metab., 300, E243.
92. Samson, S. L., Pownall, H. J., Scott, L. W., Ballantyne, C. M., Smith, E. O., Sekhar, R. V., and Balasubramanyam, A. 2006, Contemp. Clin. Trials, 27, 518.
93. Wilk, S., Scheibenbogen, C., Bauer, S., Jenke, A., Rother, M., Guerreiro, M., Kudernatsch, R., Goerner, N., Poller, W., Elligsen-Merkel, D., Utku, N., Magrane, J., Volk, H. D., and Skurk, C. 2011, Eur. J. Immunol., 41, 2323.
94. Pang, T. T. and Narendran, P. 2008, Annals of the New York Academy of Sciences, 1150, 143.
95. Neumeier, M., Weigert, J., Schaffler, A., Wehrwein, G., Muller-Ladner, U., Scholmerich, J., Wrede, C., and Buechler, C. 2006, J. Leukoc. Biol., 79, 803.
96. Ohashi, K., Parker, J. L., Ouchi, N., Higuchi, A., Vita, J. A., Gokce, N., Pedersen, A. A., Kalthoff, C., Tullin, S., Sams, A., Summer, R., and Walsh, K. 2010, The Journal of Biological Chemistry, 285, 6153.
97. Lovren, F., Pan, Y., Quan, A., Szmitko, P. E., Singh, K. K., Shukla, P. C., Gupta, M., Chan, L., Al-Omran, M., Teoh, H., and Verma, S. 2010, Am. J. Physiol. Heart Circ. Physiol., 299, H656.
98. Kachko, I., Maissel, A., Mazor, L., Ben-Romano, R., Watson, R. T., Hou, J. C., Pessin, J. E., Bashan, N., and Rudich, A. 2009, Endocrinology, 150, 2618.
99. Germinario, R. J., Colby-Germinario, S. P., Cammalleri, C., Wainberg, M. A., Koster, J. C., Remedi, M. S., Qiu, H., Nichols, C. G., and Hruz, P. W. 2003, The Journal of Endocrinology, 178, 449.
100. Belotto, M. F., Magdalon, J., Rodrigues, H. G., Vinolo, M. A., Curi, R., Pithon-Curi, T. C., and Hatanaka, E. 2010, Clin. Exp. Immunol., 162, 237.
101. Mitrou, P., Boutati, E., Lambadiari, V., Tsegka, A., Raptis, A. E., Tountas, N., Economopoulos, T., Raptis, S. A., and Dimitriadis, G. 2010, Eur. J. Endocrinol., 162, 121.
102. Mikhail, N. and Cope, D. 2005, Arch. Intern. Med., 165, 2536.
103. Anuurad, E., Bremer, A., and Berglund, L. 2010, Curr. Opin. Endocrinol. Diabetes Obes., 17, 478.
104. Tomaka, F., Lefebvre, E., Sekar, V., Van Baelen, B., Vangeneugden, T., Vandevoorde, A., and Diego Miralles, G. 2009, HIV Med., 10, 318.
105. Guaraldi, G., Zona, S., Orlando, G., Carli, F., Stentarelli, C., Luzi, K., Garlassi, E., Menozzi, M., Bagni, P., and Adorni, F. 2011, Clin. Drug Investig., 31, 759.
106. Charles, M. A., Eschwege, E., Thibult, N., Claude, J. R., Warnet, J. M., Rosselin, G. E., Girard, J., and Balkau, B. 1997, Diabtologia, 40, 1101.
107. Galbo, T., Olsen, G. S., Quistorff, B., and Nishimura, E. 2011, PLoS One, 6, e27424.
108. Minami, R., Yamamoto, M., Takahama, S., Ando, H., Miyamura, T., and Suematsu, E. 2011, Journal of Infection and Chemotherapy, 17, 183.
109. Yilmaz, S., Boffito, M., Collot-Teixeira, S., De Lorenzo, F., Waters, L., Fletcher, C., Back, D., Pozniak, A., Gazzard, B., and Mcgregor, J. L. 2010, Genomics, 96, 57.
110. Hazan, U., Romero, I. A., Cancello, R., Valente, S., Perrin, V., Mariot, V., Dumonceaux, J., Gerhardt, C. C., Strosberg, A. D., Couraud, P. O., and Pietri-Rouxel, F. 2002, The FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology, 16, 1254.