Published in final edited form as:

Curr HIV/AIDS Rep. 2018 February ; 15(1): 60–71. doi:10.1007/s11904-018-0378-z.

HIV Persistence in Adipose Tissue Reservoirs

Jacob Couturier, PhD and

Division of Infectious Diseases, Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, Texas

Dorothy E. Lewis, PhD

Division of Infectious Diseases, Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, Texas

Abstract

Purpose of review—The purpose of this review is to examine the evidence describing adipose tissue as a reservoir for HIV-1 and how this often expansive anatomic compartment contributes to HIV persistence.

Recent findings—Memory CD4 T cells and macrophages, the major host cells for HIV, accumulate in adipose tissue during HIV/SIV infection of humans and rhesus macaques. Whereas HIV and SIV proviral DNA is detectable in CD4 T cells of multiple fat depots in virtually all infected humans and monkeys examined, viral RNA is less frequently detected, and infected macrophages may be less prevalent in adipose tissue. However, based on viral outgrowth assays, adipose-resident CD4 T cells are latently infected with virus that is replication-competent and therefore infectious. Additionally, adipocytes interact with CD4 T cells and macrophages to promote immune cell activation and inflammation which may be supportive for HIV persistence. Antiviral effector cells such as CD8 T cells and NK/NKT cells are abundant in adipose tissue during HIV/SIV infection and typically exceed CD4 T cells, whereas B cells are largely absent from adipose tissue of humans and monkeys. Additionally, CD8 T cells in adipose tissue of HIV patients are activated and have a late differentiated phenotype, with unique TCR clonotypes of less diversity relative to blood CD8 T cells. With respect to the distribution of antiretroviral drugs in adipose tissue, data is limited, but there may be class-specific penetration of fat depots.

Summary—The trafficking of infected immune cells within adipose tissues is a common event during HIV/SIV infection of humans and monkeys, but the virus may be mostly transcriptionally dormant. Viral replication may occur less in adipose tissue compared to other major reservoirs such as lymphoid tissue, but replication-competence and infectiousness of adipose latent virus is comparable to other tissues. Due to the ubiquitous nature of adipose tissue, inflammatory interactions amongst adipocytes and CD4 T cells and macrophages, and selective distribution of

Corresponding Author: 6431 Fannin St., MSB 2.112 Houston, TX 77030, dorothy.e.lewis@uth.tmc.edu.

Compliance with Ethics Guidelines

Conflict of Interest

The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

antiretroviral drugs, the sequestration of infected immune cells within fat depots likely represents a major challenge for cure efforts.

Keywords

Adipose tissue; Antiretroviral therapy; CD4 T cells; HIV reservoir; Immunometabolism; Obesity

Introduction

HIV is a uniquely challenging pathogen for humans due to its high replication capacity and mechanisms of evading antiviral immunity in the absence of antiretroviral therapies (ART). In addition, the ability to cease replication and become latent in CD4 T cells (mainly memory CD4 T cells) and macrophages during virally suppressive ART allows escape from the immune response. Infected memory CD4 T cells and macrophages are constantly trafficking throughout lymphoid and non-lymphoid tissues, and depending on the tissue microenvironment, the HIV provirus can re-initiate replication or remain latent. Lymphoid tissues, particularly lymph nodes, spleen, and gut-associated lymphoid tissues (GALT) comprise major tissue reservoirs for HIV, but other tissues such as brain, lungs, liver, bone marrow, and reproductive tissues also represent important reservoir sites with unique immunological and pharmacological sanctuary characteristics that promote HIV persistence.

More recently, in large part due to increasing research interest on obesity and metabolic disorders and associated chronic inflammation, adipose tissue has been investigated as a reservoir for HIV-infected immune cells. Following seminal reports demonstrating significant accumulation of macrophages and T cells in adipose tissue in murine models of obesity, further studies of adipose-resident immune cells provided strong rationale that such immunological phenomena could be important for HIV pathogenesis and reservoir dynamics [1, 2]. Earlier studies showed that interactions between immune cells and adipocytes, specifically perinodal adipocytes, promote immune activation and adipose inflammation, suggesting adipocyte regulation of HIV replication and pathogenesis [3, 4]. Although adipose tissue health and function in HIV patients has been extensively studied over the couple of decades, particularly in the context of antiretroviral therapy and metabolism, studies more directly focused on immune cells and HIV infection in adipose tissue have only recently been reported. An overview of these studies is provided in Table 1, which provides clear evidence of HIV and SIV reservoir establishment in adipose tissue of humans and monkeys. This review examines the evidence describing adipose tissue as reservoirs for HIV and the elements that make this compartment an important contributor of persistent HIV.

Adipose tissue: a reservoir for diverse microbes

Although the primary focus of this review is HIV in adipose tissue, it is important to note that adipose tissue harbors other pathogens, particularly parasites and bacteria, each deriving benefit from and affecting adipocytes in unique ways. Parasites such as *Trypanosoma cruzi*, *Trypanosoma brucei*, and *Plasmodium* spp. infiltrate adipose tissue and reside in extracellular spaces or directly infect adipocytes of humans or mice, which have been excellently reviewed [5, 6]. A number of studies have described infection of human and

murine adipocytes by bacteria including *Mycobacterium tuberculosis*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Rickettsia prowazekii* [7–12]. With respect to viruses, cytomegalovirus and adenovirus 36 can infect human, murine, or primate adipocyte progenitor stem cells and mature adipocytes, and Adv36 infection has been associated with weight gain and obesity [13–19]. The consequences of these pathogens residing in adipose tissue is to increase adipocyte inflammation and dysfunction, immune cell activation, long-term microbial persistence, and protection from anti-microbial compounds. The microbial composition in adipose tissue, particularly visceral fat, is further altered because of intestinal breaching and microbial translocation [20–22]. It remains to be determined whether the coexistence of other pathogens with HIV in adipose tissue places additional burdens on adipocyte function and metabolic health.

Establishment of HIV reservoirs in adipose tissue and viral activity

Adipose tissue is categorized as mainly subcutaneous or visceral depots, with other minor depots uniquely associated with critical tissues and organs such as lymph nodes (perinodal fat) and the heart (pericardial and epicardial fat). Adipose tissue contains mature adipocytes and stromal-vascular-fraction cells (AT-SVF cells) which includes preadipocytes, mesenchymal stem cells, and immune cells, and this cellular composition changes significantly during disease and metabolic disorders, most notably obesity. T cells and macrophages constitute the majority of immune cells in adipose tissue, but virtually every type of innate and adaptive immune cell resides in adipose tissue of humans or mice depending on the disease or immunological challenge. The question of whether adipose tissue harbors HIV was first addressed by Dupin et al. in 2002 [23•]. Lysates of whole adipose tissue samples of twenty-three antiretroviral-treated HIV patients were examined for viral DNA by nested PCR and for RNA by conventional real-time PCR viral load assays. Only two patients were positive for HIV DNA, and none were positive for HIV RNA in adipose tissue samples. However, this study was published prior to the initial reports demonstrating the presence of macrophages and T cells in adipose tissue in mouse models of obesity, and before methods to study adipose tissue and specific cellular subsets, such as separation of adipocytes and AT-SVF cells, were better developed [1, 2]. Murine models would later demonstrate migration of immune cells into adipose tissue to become major regulators of adipocyte function and metabolism, and studies of healthy and diseased humans further showed significant accumulation of immune cells [24–27]. Additionally, virion-free circulating HIV proteins such as vpr, nef, and tat were shown to mediate detrimental effects on adipose tissue health and systemic metabolism [28–35]. In light of findings such as these and the need to better understand HIV tissue reservoirs and latency, the question of HIV persistence in adipose tissue is of high significance.

HIV or SIV proviral DNA and RNA is present mainly in CD4 T cells in adipose tissue of infected humans or monkeys, and viral DNA is replication-competent and infectious [36–40]. Obtaining adequate amounts of adipose tissue to fully characterize virological and immunological parameters is a technical limitation, as CD4 T cells typically constitute less than approximately 5–10% of AT-SVF cells in healthy humans, and AT-SVF cells constitute less than 50% of cells in a gram of adipose tissue with the majority being mature adipocytes. Current data suggests that virtually every infected human or monkey harbors infected

immune cells in both subcutaneous and visceral adipose tissue based on sensitive PCR assays for viral DNA [36••, 37••]. Using nested PCR, Couturier et al. detected HIV proviral DNA in subcutaneous and visceral AT-SVF cells in five out of five HIV patients examined when sampling at least $\sim 1 \times 10^5$ AT-SVF cells (four were cART treated) [36]. In a separate study, SHIV-SF162p3 DNA was observed in AT-SVF cells ($\sim 2 \times 10^5$ cells) in eight out of eight rhesus macaques examined after four weeks infection and not treated with antiretroviral drugs [38••]. In eleven out of eleven cART-treated HIV patients examined, Damouche et al. detected HIV DNA in visceral AT-SVF cells using ultrasensitive PCR assays, and further found viral DNA copies to be higher in adipose tissue CD4 T cells compared to blood CD4 T cells [37]. They additionally observed SIVmac251 DNA in subcutaneous and visceral AT-SVF cells in eight out of eight cynomolgus macaques that were chronically infected (fifteen months) and not treated with antiretrovirals. SIV DNA levels in adipose tissue CD4 T cells were similar to CD4 T cells in blood and lymph nodes. The investigation by Damouche et al. is also the only study to examine infected macrophages (CD14+) in adipose tissue, which were significantly less frequent compared to infected CD4 T cells in adipose tissue of SIV-infected monkeys [37]. Most recently, the presence of latently infected CD4 T cells in subcutaneous adipose tissue of cART-treated HIV patients was reported by Koethe et al. using digital droplet PCR when at least 5×10^3 CD4 T cells were examined, and consistent with the findings of Damouche et al., the DNA copy number was higher in adipose tissue CD4 T cells compared to blood CD4 T cells [40••]. The use of viral outgrowth assays to reactivate latent virus in adipose-resident CD4 T cells of HIV/SIV-infected humans and monkeys also confirmed that virus is replication-competent and infectious, and furthermore suggested that the reactivated virus in adipose tissue CD4 T cells may be more infectious relative to infected CD4 T cells in peripheral blood [37, 38]. To further determine if adipose tissue virus represents a viral species distinct from that of blood in HIV patients, gag and env genes of proviral DNA in adipose-resident CD4 T cells were sequenced by Couturier et al., but resulted in inconclusive results in part due to low subject numbers and technical limitations [36]. Additionally, sequencing of SHIV gag and env genes from acutely infected (four weeks infection) rhesus macaques resulted in identical sequences amongst subcutaneous and visceral adipose tissue virus, likely due to the clonal virus stock utilized for infection, short infection period, and minimal levels of viral evolution in SHIV-infected monkeys as observed by others [38]. Thus, whether HIV in adipose tissue represents a unique viral reservoir distinct from virus in blood or lymphoid tissues requires further study.

Although the seeding of adipose tissue by infected immune cells appears to be a definitive early event during HIV/SIV infection, viral replication in adipose tissue immune cells may be relatively infrequent and likely differs depending on the adipose tissue depot, timing of infection, and viral strain (SIV vs. SHIV). In the SIV-infected monkeys, Damouche et al. observed by RT-PCR similar levels of RNA amongst AT-SVF cells and CD4 T cells and macrophages in adipose tissue, blood, and lymph nodes, whereas in cART-treated HIV patients, detection of viral RNA in adipose tissue by in situ hybridization was much lower [37]. Consistent with the low-level detection of viral RNA in adipose tissue of HIV patients, Hsu et al. more recently observed in six SHIV-infected rhesus macaques (two or thirty weeks infection) by RNAscope that infected CD4 T cells were sparsely distributed

throughout subcutaneous and visceral adipose tissue with infrequent detection [39••]. Measurement of RNA by RT-PCR additionally showed that SHIV RNA was significantly lower in adipose tissue samples compared lymph node and intestinal tissues, whereas viral DNA was not measured. The use of humanized mouse models to study adipose tissue during HIV infection is yet to be conducted, but may be useful in further characterizing immune cells, viral replication, and antiretroviral distribution in adipose tissue, although the obvious concern with respect to studying adipocyte-immune cell interactions is the adipocytes being of murine origin.

Lastly, although many non-hematopoietic cells such as epithelial cells and astrocytes can be productively infected by HIV to minor extents, human preadipocytes and adipocytes do not express the HIV entry receptors CD4, CCR5, and CXCR4 and are incapable of being productively infected [38, 41]. Additionally, by contrast to bone marrow hematopoietic stem cells which can be infected with HIV, mesenchymal stem cells derived from human adipose tissue do not support productive HIV infection, although they can be productively infected if differentiated into hematopoietic cells [42]. Thus, CD4 T cells and macrophages are likely to be the only cells infected with HIV in adipose tissue. Altogether, these findings suggest that HIV/SIV-infected CD4 T cells, and to a lesser extent infected macrophages, accumulate in adipose tissue during acute and chronic infection despite antiretroviral treatment, but may persist mostly in a transcriptionally dormant state, which is problematic for HIV cure efforts that rely on viral reactivation.

Composition and functions of immune cells in adipose tissue during HIV/SIV infection and impact on adipocyte health and metabolism

The phenotypes and functions of CD4 and CD8 T cells, macrophages, natural killer, and NKT cells in adipose tissue of HIV/SIV-infected humans or monkeys have been studied, although the specific subsets of adipose-resident CD4 T cells and macrophages infected with HIV are not as well-characterized as for those in tissues such as lymph nodes (ie. CD4+CXCR5+PD1+ T follicular helper cells). A number of studies have described B cell accumulation in adipose tissue of obese mice and humans, but B cells have not been extensively studied in adipose tissue of HIV patients or infected monkeys [37, 38, 43–45]. Additionally, dendritic cells and granulocytes such as neutrophils, eosinophils, and mast cells infiltrate adipose tissue and regulate adipocyte function and metabolism in mice and humans, but the presence of these cells in adipose tissue during HIV/SIV infection has not been determined [46–51]. Another outstanding question pertains to the signals and chemoattractants mediating infiltration of infected immune cells into adipose tissue during HIV infection, although studies of mice and humans suggest a number of chemokine receptors including CXCR3, CCR1, CCR2, CCR5, CCR6, and CCR7 are important for T cell and macrophage migration and retention in adipose tissue [52–60].

Current information of the composition of immune cells in adipose tissue of HIV/SIV-infected humans and monkeys indicate an abundance of CD8 T cells and NK/NKT cells and macrophages, and decreased or unchanged levels of CD4 T cells. In HIV/SIV-infected humans and monkeys, T cells in adipose tissue are virtually all memory phenotype T cells

(CD45RO+ in humans or CD95+ in monkeys), and the ratio of CD4 to CD8 T cells is decreased in subcutaneous and visceral adipose depots due to increased accumulation of CD8 T cells more so than CD4 T cell depletion or apoptosis [36–38, 40, 61]. CD4 and CD8 T cells in adipose tissue of infected humans and monkeys are predominantly proinflammatory in nature based on their production of IL2, IFN γ , TNF α , and IL17A [38]. We have additionally observed the absence of IL4- and IL10-producing T cells in adipose tissue of HIV/SIV-infected humans and monkeys (unpublished observations). However, the specificity and antiviral function of CD8 T cells against infected cells in adipose tissue is yet to be studied. Damouche et al. extensively characterized T cells in adipose tissue of infected humans and monkeys and observed that CD4 T cells in SIV-infected monkeys are predominantly of central memory phenotype, whereas CD8 T cells are mainly effector memory [37, 61••]. By contrast to uninfected monkeys, adipose tissue T cells also expressed higher levels of HLA.DR indicating increased activation compared to blood T cells, yet Ki67 levels were similar between blood and adipose-resident T cells [37]. Tregs in adipose tissue are reduced in obese humans and mice, but in cART-treated HIV patients, Damouche et al. observed an increase in CD4+CD25+Foxp3+ Tregs and a higher Treg/Th17 ratio in subcutaneous adipose tissue compared to uninfected subjects [61–64]. Intriguingly, CD4 T cells in adipose tissue of HIV patients also had increased expression of PD-1 compared to blood CD4 T cells, indicating the potential immune exhaustion of adipose-resident T cells, and it was suggested that these cells may harbor latent HIV [61]. CD4 T cells in adipose tissue of obese mice also upregulate PD-1, suggesting adipose-resident T cells may develop similar phenotypes and functions during obesity and HIV infection [65]. Consistent with the expression of PD-1 by adipose tissue T cells, Koethe et al. observed that expression of CD57, a marker of late differentiation and T cell senescence, by adipose tissue T cells was increased compared to blood T cells in HIV patients [40]. Most notably in the study by Koethe et al., TCR repertoires of blood and fat CD8 T cells were studied and adipose tissue CD8 T cells had less TCR diversity compared to blood CD8 T cells, suggesting that unique antigenic signals or metabolic mediators may play a role in determining CD8 T cell trafficking and composition in adipose tissue of HIV patients. This observation is also consistent with the finding of Yang et al. who showed that TCR diversity was reduced in obese mice [66]. Functional NK and NKT cells expressing CD16, CD27, CD56, and granzymes A and B have also been observed in adipose tissue of SIV-infected monkeys by Couturier et al., suggesting increased capacity for antiviral immunity in adipose tissue [38]. Type I and II innate lymph cells (ILC) are other innate immune cells recently demonstrated to mediate adipose dysfunction, inflammation, and insulin resistance in mouse models of obesity and atherosclerosis [67–69]. Intriguingly, Boulouvar et al. also showed that type 1 ILC's, which are similar in function to NK cells, in adipose tissue of lean humans and mice have the additional function of killing adipose macrophages, perhaps to maintain adipose homeostasis. This immune clearance function of Type I ILC's is further impaired during obesity [68]. ILC's in peripheral blood and intestinal tissues undergo significant reductions during HIV/SIV infection, but the presence and function of ILC's in adipose tissue of HIV patients have not been studied [70–72]. The abundance and functions of ILC's and other innate immune cells such as NK/NKT cells in lean and obese adipose tissue are also likely to have important roles for adipose tissue homeostasis during viral infections.

Lastly, accumulation of CD68+ and CD14+ macrophages has been described in adipose tissue of HIV/SIV-infected humans and monkeys [37–39, 73–75]. In SIV-infected monkeys, Damouche et al. characterized adipose tissue macrophages and observed accumulation of CD206+CD163+ M2 anti-inflammatory macrophages [37]. In addition, the proportion of CD206-CD163- proinflammatory macrophages was increased compared to uninfected monkeys. In concert with the HIV/SIV RNA evidence indicating low levels of viral replication in adipose tissue CD4 T cells, these studies suggest that mechanisms of antiviral immunity may be adequate in controlling viral replication, although not sufficient to prevent viral reservoir establishment or to eradicate infected immune cells from adipose tissue. Other mechanisms of antiviral immunity including TLR signaling and type I interferons are also likely to contribute towards viral suppression in adipose tissue.

Despite the viral RNA data suggesting that minimal levels of HIV replication occur in adipose tissue CD4 T cells, and the infected human and monkey data suggesting that adipose-resident T cells overall may undergo less activation relative to T cells in other tissues, in vitro and in vivo studies show that adipocytes can stimulate adipose-resident T cells to promote HIV replication. In vitro co-culture experiments between HIV-infected CD4 T cells and primary human adipocytes show that adipocytes enhance IL2-, IL7-, or IL15-induced T cell activation and HIV replication, mediated by IL6 and integrin ligands [36]. Adipose tissue macrophages activate adipose-resident CD4 T cells via class II MHC, but more surprisingly, adipocytes of obese humans and mice also express class II MHC and activate adipose-resident CD4 T cells [76–79]. In vitro co-culture studies between human adipocytes and CD4 T cells causes increased T cell activation and proliferation also mediated in part by class II MHC mechanisms, as well as free fatty acids [80, 81]. Adipocytes also release exosomes which regulate metabolic pathways and disease pathogenesis, and separate studies have additionally shown that exosomes can reactivate latent HIV in CD4 T cells [82–87].

The consequences of HIV replication in adipose-resident immune cells for adipocyte function are implicated by a number of studies demonstrating that soluble viral proteins such as vpr, nef, and tat negatively impact adipocyte biology. The HIV accessory protein vpr has been the most extensively studied with respect to their effects on adipocyte function. Shrivastav et al. showed that vpr transduces 3T3-L1 murine preadipocytes, antagonizes PPAR γ function, and suppresses expression of critical adipocyte differentiation genes [88]. In mouse models exposed to vpr via transgenic expression, direct injections, or ALZET osmotic pumps, Balasubramanyam et al. and Agarwal et al. further demonstrated that vpr impairs adipocyte growth and function, increases adipose inflammation, dysregulates systemic lipid metabolism, and promotes fatty liver disease [28, 33, 34]. Importantly for HIV-infected quiescent CD4 T cells in different tissue reservoirs, circulating vpr can also reactivate latent provirus [89, 90]. Adipocytes exposed to tat and nef in vitro also result in suppression of PPAR γ function and adipogenesis, as well as the upregulation of inflammatory cytokines and impairment of glucose uptake [29, 31, 32]. In SIV-infected rhesus macaques, Asztalos et al. showed that circulating nef dysregulates lipid metabolism by localizing to the liver and inhibiting cholesterol efflux pathways in infected macrophages and hepatocytes [30]. In acutely (four weeks) and chronically (38 weeks) infected rhesus macaques not treated with antiretroviral drugs, expression of genes critical for adipocyte

function including C/EBP α , leptin, and GLUT4 were downregulated compared to uninfected monkeys [38]. Infected monkeys additionally experienced dyslipidemias as indicated by altered serum levels of triglycerides and free fatty acids, consistent with metabolic abnormalities in HIV patients. In chronically infected macaques, Damouche et al. showed that the density of adipocytes and AT-SVF cells were significantly increased compared to uninfected monkeys, suggestive of abnormal patterns of growth and differentiation of fat cells [37]. Antiretrovirals are major regulators of adipose tissue function and metabolism in HIV patients, but in light of the recent studies demonstrating establishment of HIV reservoirs in adipose tissue and the potential proviral induction capacity by adipocytes, the mechanisms of adipocyte dysfunction mediated directly by infected immune cells and soluble viral proteins have become more important.

Antiretroviral therapy and adipose tissue

Systemic distribution of HIV antiretroviral drugs is critical for viral suppression, and the improvement of antiretroviral pharmacology and modes of delivery are intensely investigated. Despite the successes of cART, latently infected immune cells persist in pharmacological sanctuary sites such as lymph nodes, GALT, brain, and reproductive tissues, such that HIV likely undergoes transient low-level replication. In lymph nodes of cART-treated patients, viral persistence is associated with lower levels of antiretroviral drug penetration relative to other tissues such as PBMC and serum, and in the brain, certain drugs are excluded by the blood-brain barrier. For example, Fletcher et al. showed that the intracellular concentrations of nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir and emtricitabine), non-nucleoside reverse transcriptase inhibitor (efavirenz), and protease inhibitors (atazanavir and darunavir) in lymph nodes of HIV patients were all significantly lower compared to PBMCs, and these lower drug levels were further associated with viral replication in lymph nodes [91]. Whether adipose tissue represents a pharmacological sanctuary for HIV is currently unclear, but available evidence suggests the possibility depending on the antiretroviral regimen.

The impact of antiretroviral therapy upon adipose tissue health and metabolism is extensively studied, but the study by Dupin et al. is the only study which directly investigated drug distribution in adipose tissue of HIV patients [23]. In the study, lysates of whole adipose tissue samples were examined by LC/MS for the presence of protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), and non-nucleoside reverse transcriptase inhibitors (NNRTI). Integrase inhibitors (INSTI) were not examined as this study was conducted prior to FDA approval for raltegravir in 2007. A clear drug class-specific distribution was observed in which NRTI's were below detection limits in adipose tissue samples of all patients, levels of PI's were minimal to undetectable (<2 nmol/g), and NNRTI's were present in significant amounts (~38–285 nmol/g). The authors of the present review are also currently investigating antiretroviral distribution in adipose tissue of HIV patients and SHIV-infected rhesus monkeys and have obtained similar data (unpublished observations). Consistent with the findings of Dupin et al. in which whole adipose tissue lysates were studied, we have observed a lack of N(t)RTI penetration in BOTH separated adipocytes and AT-SVF samples of HIV patients and rhesus monkeys, whereas NNRTI's were detectable in fat samples. Most intriguingly, we have observed significant penetration

of INSTI's such as dolutegravir and elvitegravir in adipocytes and AT-SVF cells (a subject on raltegravir has not yet been studied), which in conjunction with the findings of Dupin et al. suggest that NNRTI's and INSTI's enter adipose tissue, whereas PI's and N(t)RTI's are more restricted. We have additionally observed in in vitro co-culture experiments that adipocytes can negatively affect antiretroviral efficacy, mediated in part by significant uptake and sequestration of drugs by adipocytes, consistent with other in vitro studies demonstrating rapid and significant uptake of antiretrovirals by adipocytes [92, 93].

Intriguingly, Damouche et al. showed that CD4 T cells in adipose tissue of SIV-infected monkeys were localized significantly more distal to blood vessels compared to CD8 T cells, suggesting that distribution of antiretroviral drugs to infected CD4 T cells could be more challenging, particularly if drugs are rapidly sequestered and metabolized by adipocytes and other AT-SVF cells [37]. Significant uptake of antiretroviral drugs by adipocytes would be another impediment for drug distribution as adipocytes can accumulate in HIV reservoir sites such as lymph nodes, bone marrow, liver, and GALT. Expression of drug transporters by adipocytes, AT-SVF cells, and adipose-resident immune cells is another consideration for drug distribution as these cells express influx and efflux transporters including P-glycoprotein, multidrug resistance proteins, equilibrative nucleoside transporters, and breast cancer resistance proteins which regulate cellular antiretroviral uptake and retention [94–97]. Antiretroviral pharmacology is regulated by a number of factors including half-life, protein binding, lipophilicity, intracellular metabolism, and drug transporters, and many of these elements so far appear to be relevant in adipose tissue.

In the context other microbial infections and diseases, adipocytes reduce the efficacy of therapeutic compounds. For example, *M. tuberculosis* and *T. cruzi* persist in adipose tissue of humans and mice despite antibiotic treatments [7, 11, 12, 98]. Neyrolles et al. and Beigier-Bompadre et al. have shown persistence of *M. tuberculosis* in adipose tissue of humans. Agarwal et al. showed that anti-tubercular drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) significantly reduced *M. tuberculosis* in lungs and kidneys of mice, whereas bacterial levels in different adipose depots were modestly affected, and Francisco et al. demonstrated persistence of *T. cruzi* in visceral adipose tissue of mice treated with the antifungal posaconazole [11, 98]. Lastly, extensive research has established that adipocytes significantly influence tumor progression and cancer biology [99–101]. Adipocytes cross-talk with tumor cells to promote growth and metastases, and further enhance chemotherapeutic resistance by impairing mechanisms of tumor cell killing and sequestering drugs. For example, trastuzumab is a critical antibody-based chemotherapeutic against breast cancer which mediates tumor cell killing by natural killer cells and ADCC mechanisms, and adipocytes suppress such tumor cell killing by secreting factors that impair NK cell functions [102]. Additionally, daunorubicin is another important chemotherapeutic for leukemias and adipocytes enhance survival of acute lymphoblastic leukemia cells by secreting factors which protect the tumor cells from oxidative stress, as well as by accumulating and inactivating significant amounts of daunorubicin [103, 104]. Lastly, human T-cell acute lymphoblastic leukemia (T-ALL) cancer cells transplanted into mice accumulate in gonadal adipose tissue of mice and adopt enhanced chemoresistance profiles similar to T-ALL cells in bone marrow sites rich in adipocytes, and adipose T-ALL cells furthermore became more resistant to vincristine when co-cultured with adipocytes in vitro

[105]. These studies further highlight the dynamic nature of adipocytes and interaction with other cells beyond metabolism.

The characterization of adipose tissue as a pharmacological sanctuary for HIV requires further investigation, but available evidence suggests that penetration of antiretroviral drugs into adipose tissue is class-specific, in which NNRTI's and INSTI's may be significantly more fat-soluble compared to PI's and N(t)RTI's. This is important for the HIV reservoir in adipose tissue as N(t)RTI's typically constitute the "backbone" of most antiretroviral regimens. The distribution and pharmacology of antiretroviral drugs in adipose tissue continues to be investigated in our laboratory, as well as in ongoing clinical trials being conducted by other investigators, and the findings from these studies will enhance our understanding of antiretroviral pharmacology, particularly in lipid-rich tissues with high metabolic activity. Additionally, as it is now clear that adipose tissue harbors latently infected immune cells, it will also be important to better understand the adipose tissue distribution of other therapeutics currently being tested as part of HIV cure strategies such as HDAC inhibitors, TLR agonists, or nanoformulated antiretrovirals.

Immunometabolism, metabolic reprogramming and relevance for HIV tissue reservoirs

The recent heightened interest in metabolism, immunometabolism, and metabolic disorders such as obesity and diabetes have led to new concepts with potentially significant relevance for HIV immunology and virology, particularly HIV-infected immune cells in different tissue reservoirs which differ in the regulation of viral replication and latency. Generally, immunometabolism and metabolic reprogramming refer to the regulation of immune cell development, differentiation, and function by systemic metabolism and intracellular metabolic pathways - more specifically, major bioenergetic pathways including glycolysis, oxidative phosphorylation, and fatty acid oxidation and lipid metabolism [106–113]. These topics have been extensively reviewed and studied mostly in the context of cancer immunology, but recent studies have begun to demonstrate their importance for HIV replication and pathogenesis. Hegedus et al. showed that glycolysis is essential for HIV replication in primary human CD4 T cells [114]. Extensive studies by the Palmer and Crowe groups have investigated how metabolic pathways such as glucose metabolism and glycolysis influence human T cell and monocyte function and homeostasis, and susceptibility to HIV infection [115–119]. Activation of mTOR, a major regulator of metabolic pathway utilization and T cell activation, was recently demonstrated by Besnard et al. to be essential for induction of latent HIV in human CD4 T cells [120]. Rasheed et al. showed that HIV replication upregulates lipid metabolism pathways and production of free fatty acids in infected human CD4 T cells, and consistent with this study, Angela et al. showed that fatty acid metabolism through mTOR and PPAR γ activation is critical for maximal activation of human CD4 T cells [121, 122]. CD4 T regulatory cells, important regulators of adipose tissue homeostasis as well representing a cellular reservoir for latent HIV, preferentially utilize oxphos and recent studies have demonstrated that Foxp3 promotes activation of oxphos and fatty acid oxidation pathways [123–126]. The importance of metabolism for HIV pathogenesis is further highlighted by an earlier report by Mansfield et

al. demonstrating increased disease progression and death of SIV-infected rhesus macaques fed a high-fat diet of cholesterol and saturated fatty acids [127]. Thus, these metabolic pathways represent another level of epigenetic control of T cell function and survival beyond immunological signals that may explain some differences with respect to HIV replication and persistence in non-lymphoid tissue reservoirs such as adipose tissue. In mice and monkeys, we have observed significant differences in glycolytic and oxphos metabolic phenotypes amongst T cells in lymphoid and metabolic tissues including blood, lymph nodes, spleen, liver, and adipose tissues (unpublished observations). How these metabolic states influence viral replication versus latency in different tissue reservoirs are the subject of ongoing studies. As these metabolic pathways and mechanisms of immune regulation continue to be elucidated, it may be transformative to see how application to the HIV field enhances understanding of viral replication, latency, and persistence in tissue reservoirs, as well as advance new therapeutic options.

Conclusions

Traditionally regarded as simple connective tissue with important metabolic functions, the recent explosion of research into metabolism, obesity, immunometabolism, and molecular endocrinology have revealed that adipose tissue is highly dynamic and major regulators of not only metabolism, but immunology, cancer, and microbial pathogenesis. The fact that adipose tissue and adipocytes are often in such intricate association with important HIV tissue reservoirs such as lymph nodes, GALT, liver, thymus, and bone marrow suggests an important role of fat depots for T cell dynamics, HIV pathogenesis, and antiretroviral efficacy in these reservoir sites, and the HIV field will continue to benefit from intensive ongoing research into obesity and metabolism. Future research into the adipose tissue HIV reservoir will hopefully yield more insight into viral latency and replication dynamics in adipose tissue, the contribution of the adipose tissue reservoir to the total body viral load, how the viral reservoir impacts adipose tissue health and function, immunological responses and control of adipose tissue virus, antiretroviral pharmacology in adipose tissue, and the role of metabolic reprogramming of infected immune cells in lymphoid and non-lymphoid tissues.

References

1. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003; 112:1796–808. DOI: 10.1172/JCI19246 [PubMed: 14679176]
2. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest.* 2003; 112:1821–30. DOI: 10.1172/JCI19451 [PubMed: 14679177]
3. Pond CM, Mattacks CA. The activation of the adipose tissue associated with lymph nodes during the early stages of an immune response. *Cytokine.* 2002; 17:131–9. DOI: 10.1006/cyto.2001.0999 [PubMed: 11895331]
4. Pond CM. Paracrine relationships between adipose and lymphoid tissues: implications for the mechanism of HIV-associated adipose redistribution syndrome. *Trends Immunol.* 2003; 24:13–8. DOI: 10.1016/S1471-4906(02)00004-2 [PubMed: 12495719]

5. Franke-Fayard B, Fonager J, Braks A, Khan SM, Janse CJ. Sequestration and tissue accumulation of human malaria parasites: can we learn anything from rodent models of malaria? *PLoS Pathog.* 2010; 6:e1001032.doi: 10.1371/journal.ppat.1001032 [PubMed: 20941396]
6. Tanowitz HB, Scherer PE, Mota MM, Figueiredo LM. Adipose Tissue: A Safe Haven for Parasites? *Trends Parasitol.* 2017; 33:276–84. DOI: 10.1016/j.pt.2016.11.008 [PubMed: 28007406]
7. Neyrolles O, Hernández-Pando R, Pietri-Rouxel F, Fornès P, Tailleux L, Barrios Payán JA, et al. Is adipose tissue a place for *Mycobacterium tuberculosis* persistence? *PLoS One.* 2006; 1:e43.doi: 10.1371/journal.pone.0000043 [PubMed: 17183672]
8. Bechah Y, Paddock CD, Capo C, Mege JL, Raoult D. Adipose tissue serves as a reservoir for recrudescence of *Rickettsia prowazekii* infection in a mouse model. *PLoS One.* 2010; 5:e8547.doi: 10.1371/journal.pone.0008547 [PubMed: 20049326]
9. Hanses F, Kopp A, Bala M, Buechler C, Falk W, Salzberger B, et al. Intracellular survival of *Staphylococcus aureus* in adipocyte-like differentiated 3T3-L1 cells is glucose dependent and alters cytokine, chemokine, and adipokine secretion. *Endocrinology.* 2011; 152:4148–57. DOI: 10.1210/en.2011-0103 [PubMed: 21914779]
10. Zulian A, Canello R, Ruocco C, Gentilini D, Di Blasio AM, Danelli P, et al. Differences in visceral fat and fat bacterial colonization between ulcerative colitis and Crohn's disease. An in vivo and in vitro study. *PLoS One.* 2013; 8:e78495.doi: 10.1371/journal.pone.0078495 [PubMed: 24205244]
11. Agarwal P, Khan SR, Verma SC, Beg M, Singh K, Mitra K, et al. *Mycobacterium tuberculosis* persistence in various adipose depots of infected mice and the effect of anti-tubercular therapy. *Microbes Infect.* 2014; 16:571–80. DOI: 10.1016/j.micinf.2014.04.006 [PubMed: 24819214]
12. Beigier-Bompadre M, Montagna GN, Kühl AA, Lozza L, Weiner J 3rd, Kupz A, et al. *Mycobacterium tuberculosis* infection modulates adipose tissue biology. *PLoS Pathog.* 2017; 13:e1006676.doi: 10.1371/journal.ppat.1006676 [PubMed: 29040326]
13. Dhurandhar NV, Whigham LD, Abbott DH, Schultz-Darken NJ, Israel BA, Bradley SM, et al. Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. *J Nutr.* 2002; 132:3155–60. [PubMed: 12368411]
14. Vangipuram SD, Yu M, Tian J, Stanhope KL, Pasarica M, Havel PJ, et al. Adipogenic human adenovirus-36 reduces leptin expression and secretion and increases glucose uptake by fat cells. *Int J Obes (Lond).* 2007; 31:87–96. DOI: 10.1038/sj.ijo.0803366 [PubMed: 16703005]
15. Rogers PM, Mashtalir N, Rathod MA, Dubuisson O, Wang Z, Dasuri K, et al. Metabolically favorable remodeling of human adipose tissue by human adenovirus type 36. *Diabetes.* 2008; 57:2321–31. DOI: 10.2337/db07-1311 [PubMed: 18599527]
16. Bouwman JJ, Diepersloot RJ, Visseren FL. Intracellular infections enhance interleukin-6 and plasminogen activator inhibitor 1 production by cocultivated human adipocytes and THP-1 monocytes. *Clin Vaccine Immunol.* 2009; 16:1222–7. DOI: 10.1128/CI.00166-09 [PubMed: 19553556]
17. Salehian B, Forman SJ, Kandeel FR, Bruner DE, He J, Atkinson RL. Adenovirus 36 DNA in adipose tissue of patient with unusual visceral obesity. *Emerg Infect Dis.* 2010; 16:850–2. DOI: 10.3201/eid1605.091271 [PubMed: 20409382]
18. Lin WY, Dubuisson O, Rubicz R, Liu N, Allison DB, Curran JE, et al. Long-term changes in adiposity and glycemic control are associated with past adenovirus infection. *Diabetes Care.* 2013; 36:701–7. DOI: 10.2337/dc12-1089 [PubMed: 23160725]
19. Zvezdaryk KJ, Ferris MB, Strong AL, Morris CA, Bunnell BA, Dhurandhar NV, et al. Human cytomegalovirus infection of human adipose-derived stromal/stem cells restricts differentiation along the adipogenic lineage. *Adipocyte.* 2015; 5:53–64. DOI: 10.1080/21623945.2015.1119957 [PubMed: 27144097]
20. Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med.* 2011; 3:559–72. DOI: 10.1002/emmm.201100159 [PubMed: 21735552]
21. Kruis T, Batra A, Siegmund B. Bacterial translocation - impact on the adipocyte compartment. *Front Immunol.* 2014; 4:510.doi: 10.3389/fimmu.2013.00510 [PubMed: 24432024]

22. Karrasch T, Schaeffler A. Adipokines and the role of visceral adipose tissue in inflammatory bowel disease. *Ann Gastroenterol.* 2016; 29:424–38. DOI: 10.20524/aog.2016.0077 [PubMed: 27708507]
- 23•. Dupin N, Buffet M, Marcelin AG, Lamotte C, Gorin I, Ait-Arkoub Z, et al. HIV and antiretroviral drug distribution in plasma and fat tissue of HIV-infected patients with lipodystrophy. *AIDS.* 2002; 16:2419–24. This was the first study to investigate the presence of HIV and antiretroviral penetration in adipose tissue. [PubMed: 12461415]
24. Schipper HS, Prakken B, Kalkhoven E, Boes M. Adipose tissue-resident immune cells: key players in immunometabolism. *Trends Endocrinol Metab.* 2012; 23:407–15. DOI: 10.1016/j.tem.2012.05.011 [PubMed: 22795937]
25. Koethe JR, Hulgán T, Niswender K. Adipose tissue and immune function: a review of evidence relevant to HIV infection. *J Infect Dis.* 2013; 208:1194–201. DOI: 10.1093/infdis/jit324 [PubMed: 23878320]
26. Mathis D. Immunological goings-on in visceral adipose tissue. *Cell Metab.* 17:851–9. 2011. DOI: 10.1016/j.cmet.2013.05.008
27. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. *Cardiovasc Res.* 2017; 113:1009–23. DOI: 10.1093/cvr/cvx108 [PubMed: 28838042]
28. Balasubramanyam A, Mersmann H, Jahoor F, Phillips TM, Sekhar RV, Schubert U, et al. Effects of transgenic expression of HIV-1 Vpr on lipid and energy metabolism in mice. *Am J Physiol Endocrinol Metab.* 2007; 292:E40–8. DOI: 10.1152/ajpendo.00163.2006 [PubMed: 16882932]
29. Otake K, Omoto S, Yamamoto T, Okuyama H, Okada H, Okada N, et al. HIV-1 Nef protein in the nucleus influences adipogenesis as well as viral transcription through the peroxisome proliferator-activated receptors. *AIDS.* 2004; 18:189–98. [PubMed: 15075535]
30. Asztalos BF, Mujawar Z, Morrow MP, Grant A, Pushkarsky T, Wanke C, et al. Circulating Nef induces dyslipidemia in simian immunodeficiency virus-infected macaques by suppressing cholesterol efflux. *J Infect Dis.* 2010; 202:614–23. DOI: 10.1086/654817 [PubMed: 20617930]
31. Cheney L, Hou JC, Morrison S, Pessin J, Steigbigel RT. Nef inhibits glucose uptake in adipocytes and contributes to insulin resistance in human immunodeficiency virus type I infection. *J Infect Dis.* 2011; 203:1824–31. DOI: 10.1093/infdis/jir170 [PubMed: 21606541]
32. Díaz-Delfín J, Domingo P, Wabitsch M, Giral M, Villarroja F. HIV-1 Tat protein impairs adipogenesis and induces the expression and secretion of proinflammatory cytokines in human SGBS adipocytes. *Antivir Ther.* 2012; 17:529–40. DOI: 10.3851/IMP2021 [PubMed: 22301094]
33. Agarwal N, Iyer D, Patel SG, Sekhar RV, Phillips TM, Schubert U, et al. HIV-1 Vpr induces adipose dysfunction in vivo through reciprocal effects on PPAR/GR co-regulation. *Sci Transl Med.* 2013; 5:213ra164.doi: 10.1126/scitranslmed.3007148
34. Agarwal N, Iyer D, Gabbi C, Saha P, Patel SG, Mo Q, et al. HIV-1 viral protein R (Vpr) induces fatty liver in mice via LXR α and PPAR α dysregulation: implications for HIV-specific pathogenesis of NAFLD. *Sci Rep.* 2017; 7:13362.doi: 10.1038/s41598-017-13835-w [PubMed: 29042644]
35. Koethe JR. Adipose Tissue in HIV Infection. *Compr Physiol.* 2017; 7:1339–57. DOI: 10.1002/cphy.c160028 [PubMed: 28915327]
- 36••. Couturier J, Suliburk JW, Brown JM, Luke DJ, Agarwal N, Yu X, et al. Human adipose tissue as a reservoir for memory CD4+ T cells and HIV. *AIDS.* 2015; 29:667–74. This study was one of the initial reports demonstrating human adipose tissue to be a reservoir for HIV-infected immune cells. DOI: 10.1097/QAD.0000000000000599 [PubMed: 25849830]
- 37••. Damouche A, Lazure T, Avettand-Fènoël V, Huot N, Dejucq-Rainsford N, Satie AP, et al. Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection. *PLoS Pathog.* 2015; 11:e1005153. This study was one of the initial reports demonstrating that human and non-human primate adipose tissue are reservoirs for HIV/SIV-infected CD4 T cells and macrophages. doi: 10.1371/journal.ppat.1005153 [PubMed: 26402858]
- 38••. Couturier J, Agarwal N, Nehete PN, Baze WB, Barry MA, Jagannadha Sastry K, et al. Infectious SIV resides in adipose tissue and induces metabolic defects in chronically infected rhesus macaques. *Retrovirology.* 2016; 13:30. This study was one of the initial reports demonstrating

rhesus macaque adipose tissue to be a reservoir for SIV-infected immune cells. doi: 10.1186/s12977-016-0260-2 [PubMed: 27117277]

- 39••. Hsu DC, Wegner MD, Sunyakumthorn P, Silsorn D, Tayamun S, Inthawong D, et al. CD4+ Cell infiltration into subcutaneous adipose tissue is not indicative of productively infected cells during acute SHIV infection. *J Med Primatol*. 2017; 46:154–57. This study demonstrated that SHIV-infected CD4 T cells can accumulate in adipose tissue of rhesus macaques after acute infection. DOI: 10.1111/jmp.12298 [PubMed: 28748665]
- 40••. Koethe JR, McDonnell W, Kennedy A, Abana CO, Pilkinton M, Setliff I, et al. Adipose Tissue is Enriched for Activated and Late-differentiated CD8+ T cells, and Shows Distinct CD8+ Receptor Usage, Compared to Blood in HIV-infected Persons. *J Acquir Immune Defic Syndr*. 2017; In press. This study demonstrated the presence of HIV-infected CD4 T cells in human adipose tissue and further characterized the TCR repertoire of adipose tissue CD8 T cells. doi: 10.1097/QAI.0000000000001573
41. Munier S, Borjabad A, Lemaire M, Mariot V, Hazan U. In vitro infection of human primary adipose cells with HIV-1: a reassessment. *AIDS*. 2003; 17:2537–9. [PubMed: 14600528]
42. Nazari-Shafti TZ, Freisinger E, Roy U, Bulot CT, Senst C, Dupin CL, et al. Mesenchymal stem cell derived hematopoietic cells are permissive to HIV-1 infection. *Retrovirology*. 2011; 8:3.doi: 10.1186/1742-4690-8-3 [PubMed: 21226936]
43. Nishimura S, Manabe I, Takaki S, Nagasaki M, Otsu M, Yamashita H, et al. Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation. *Cell Metab*. 2013; 18:759–66. DOI: 10.1016/j.cmet.2013.09.017
44. Frasca D, Blomberg BB. Adipose Tissue Inflammation Induces B Cell Inflammation and Decreases B Cell Function in Aging. *Front Immunol*. 2017; 8:1003.doi: 10.3389/fimmu.2017.01003 [PubMed: 28894445]
45. Ying W, Wollam J, Ofrecio JM, Bandyopadhyay G, El Ouarrat D, Lee YS, et al. Adipose tissue B2 cells promote insulin resistance through leukotriene LTB4/LTB4R1 signaling. *J Clin Invest*. 2017; 127:1019–30. DOI: 10.1172/JCI90350 [PubMed: 28192375]
46. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*. 2011; 332:243–7. DOI: 10.1126/science.1201475 [PubMed: 21436399]
47. Bertola A, Ciucci T, Rousseau D, Bourlier V, Duffaut C, Bonnafous S, et al. Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. *Diabetes*. 2012; 61:2238–47. DOI: 10.2337/db11-1274 [PubMed: 22596049]
48. Divoux A, Moutel S, Poitou C, Lacasa D, Veyrie N, Aissat A, et al. Mast cells in human adipose tissue: link with morbid obesity, inflammatory status, and diabetes. *J Clin Endocrinol Metab*. 2012; 97:E1677–85. DOI: 10.1210/jc.2012-1532 [PubMed: 22745246]
49. Talukdar S, Oh DY, Bandyopadhyay G, Li D, Xu J, McNelis J, et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. *Nat Med*. 2012; 18:1407–12. DOI: 10.1038/nm.2885 [PubMed: 22863787]
50. Cho KW, Zamarron BF, Muir LA, Singer K, Porsche CE, DelProposto JB, et al. Adipose Tissue Dendritic Cells Are Independent Contributors to Obesity-Induced Inflammation and Insulin Resistance. *J Immunol*. 2016; 197:3650–61. DOI: 10.4049/jimmunol.1600820 [PubMed: 27683748]
51. Sundara Rajan S, Longhi MP. Dendritic cells and adipose tissue. *Immunology*. 2016; 149:353–61. DOI: 10.1111/imm.12653 [PubMed: 27479803]
52. Weisberg SP, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, et al. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *J Clin Invest*. 2006; 116:115–24. DOI: 10.1172/JCI24335 [PubMed: 16341265]
53. Wu H, Ghosh S, Perrard XD, Feng L, Garcia GE, Perrard JL, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation*. 2007; 115:1029–38. DOI: 10.1161/CIRCULATIONAHA.106.638379 [PubMed: 17296858]

54. Duffaut C, Zakaroff-Girard A, Bourlier V, Decaunes P, Maumus M, Chiotasso P, et al. Interplay between human adipocytes and T lymphocytes in obesity: CCL20 as an adipochemokine and T lymphocytes as lipogenic modulators. *Arterioscler Thromb Vasc Biol.* 2009; 29:1608–14. DOI: 10.1161/ATVBAHA.109.192583 [PubMed: 19644053]
55. Kitade H, Sawamoto K, Nagashimada M, Inoue H, Yamamoto Y, Sai Y, et al. CCR5 plays a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status. *Diabetes.* 2012; 61:1680–90. DOI: 10.2337/db11-1506 [PubMed: 22474027]
56. Deiluiis JA, Oghumu S, Duggineni D, Zhong J, Rutsky J, Banerjee A, et al. CXCR3 modulates obesity-induced visceral adipose inflammation and systemic insulin resistance. *Obesity (Silver Spring).* 2014; 22:1264–74. DOI: 10.1002/oby.20642 [PubMed: 24124129]
57. Rocha VZ, Folco EJ, Ozdemir C, Sheikine Y, Christen T, Sukhova GK, et al. CXCR3 controls T-cell accumulation in fat inflammation. *Arterioscler Thromb Vasc Biol.* 2014; 34:1374–81. DOI: 10.1161/ATVBAHA.113.303133 [PubMed: 24812325]
58. Conroy MJ, Galvin KC, Kavanagh ME, Mongan AM, Doyle SL, Gilmartin N, et al. CCR1 antagonism attenuates T cell trafficking to omentum and liver in obesity-associated cancer. *Immunol Cell Biol.* 2016; 94:531–7. DOI: 10.1038/icb.2016.26 [PubMed: 27046081]
59. Hellmann J, Sansbury BE, Holden CR, Tang Y, Wong B, Wysoczynski M, et al. CCR7 Maintains Nonresolving Lymph Node and Adipose Inflammation in Obesity. *Diabetes.* 2016; 65:2268–81. DOI: 10.2337/db15-1689 [PubMed: 27207557]
60. Orr JS, Kennedy AJ, Hill AA, Anderson-Baucum EK, Hubler MJ, Hasty AH. CC-chemokine receptor 7 (CCR7) deficiency alters adipose tissue leukocyte populations in mice. *Physiol Rep.* 2016; 4:e12971.doi: 10.14814/phy2.12971 [PubMed: 27655794]
61. Damouche A, Pourcher G, Pourcher V, Benoist S, Busson E, Lataillade JJ, et al. High proportion of PD-1-expressing CD4⁺ T cells in adipose tissue constitutes an immunomodulatory microenvironment that may support HIV persistence. *Eur J Immunol.* 2017; In press This study extensively phenotyped T cells in adipose tissue of HIV patients and demonstrated that significant proportions of adipose CD4 T cells may persist in states of exhaustion and quiescence. doi: 10.1002/eji.201747060
62. Deiluiis J, Shah Z, Shah N, Needleman B, Mikami D, Narula V, et al. Visceral adipose inflammation in obesity is associated with critical alterations in regulatory cell numbers. *PLoS One.* 2011; 6:e16376.doi: 10.1371/journal.pone.0016376 [PubMed: 21298111]
63. Cipolletta D. Adipose tissue-resident regulatory T cells: phenotypic specialization, functions and therapeutic potential. *Immunology.* 2014; 142:517–25. DOI: 10.1111/imm.12262 [PubMed: 24484282]
64. Deng T, Liu J, Deng Y, Minze L, Xiao X, Wright V, et al. Adipocyte adaptive immunity mediates diet-induced adipose inflammation and insulin resistance by decreasing adipose Treg cells. *Nat Commun.* 2017; 8:15725.doi: 10.1038/ncomms15725
65. Shirakawa K, Yan X, Shinmura K, Endo J, Kataoka M, Katsumata Y, et al. Obesity accelerates T cell senescence in murine visceral adipose tissue. *J Clin Invest.* 2016; 126:4626–39. DOI: 10.1172/JCI88606 [PubMed: 27820698]
66. Yang H, Youm YH, Vandanmagsar B, Ravussin A, Gimble JM, Greenway F, et al. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resistance. *J Immunol.* 2010; 185:1836–45. DOI: 10.4049/jimmunol.1000021 [PubMed: 20581149]
67. O'Sullivan TE, Rapp M, Fan X, Weizman OE, Bhardwaj P, Adams NM, et al. Adipose-Resident Group 1 Innate Lymphoid Cells Promote Obesity-Associated Insulin Resistance. *Immunity.* 2016; 45:428–41. DOI: 10.1016/j.immuni.2016.06.016 [PubMed: 27496734]
68. Boulouvar S, Michelet X, Duquette D, Alvarez D, Hogan AE, Dold C, et al. Adipose Type One Innate Lymphoid Cells Regulate Macrophage Homeostasis through Targeted Cytotoxicity. *Immunity.* 2017; 46:273–86. DOI: 10.1016/j.immuni.2017.01.008 [PubMed: 28228283]
69. Newland SA, Mohanta S, Clément M, Taleb S, Walker JA, Nus M, et al. Type-2 innate lymphoid cells control the development of atherosclerosis in mice. *Nat Commun.* 2017; 8:15781.doi: 10.1038/ncomms15781 [PubMed: 28589929]

70. Li H, Richert-Spuhler LE, Evans TI, Gillis J, Connole M, Estes JD, et al. Hypercytotoxicity and rapid loss of NKp44+ innate lymphoid cells during acute SIV infection. *PLoS Pathog.* 2014; 10:e1004551.doi: 10.1371/journal.ppat.1004551 [PubMed: 25503264]
71. Kløverpris HN, Kazer SW, Mjösberg J, Mabuka JM, Wellmann A, Ndhlovu Z, et al. Innate Lymphoid Cells Are Depleted Irreversibly during Acute HIV-1 Infection in the Absence of Viral Suppression. *Immunity.* 2016; 44:391–405. DOI: 10.1016/j.immuni.2016.01.006 [PubMed: 26850658]
72. Krämer B, Goeser F, Lutz P, Glässner A, Boesecke C, Schwarze-Zander C, et al. Compartment-specific distribution of human intestinal innate lymphoid cells is altered in HIV patients under effective therapy. *PLoS Pathog.* 2017; 13:e1006373.doi: 10.1371/journal.ppat.1006373 [PubMed: 28505204]
73. Jan V, Cervera P, Maachi M, Baudrimont M, Kim M, Vidal H, 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. [PubMed: 15456087]
74. Sievers M, Walker UA, Sevastianova K, Setzer B, Wågsäter D, Eriksson P, et al. Gene expression and immunohistochemistry in adipose tissue of HIV type 1-infected patients with nucleoside analogue reverse-transcriptase inhibitor-associated lipodystrophy. *J Infect Dis.* 2009; 200:252–62. DOI: 10.1086/599986 [PubMed: 19519254]
75. Shikuma CM, Gangcuangco LM, Killebrew DA, Libutti DE, Chow DC, Nakamoto BK, et al. The role of HIV and monocytes/macrophages in adipose tissue biology. *J Acquir Immune Defic Syndr.* 2014; 65:151–9. DOI: 10.1097/01.qai.0000435599.27727.6c [PubMed: 24091690]
76. Deng T, Lyon CJ, Minze LJ, Lin J, Zou J, Liu JZ, et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. *Cell Metab.* 2013; 17:411–22. DOI: 10.1016/j.cmet.2013.02.009 [PubMed: 23473035]
77. Morris DL, Cho KW, Delproposto JL, Oatmen KE, Geletka LM, Martinez-Santibanez G, et al. Adipose tissue macrophages function as antigen-presenting cells and regulate adipose tissue CD4+ T cells in mice. *Diabetes.* 2013; 62:2762–72. DOI: 10.2337/db12-1404 [PubMed: 23493569]
78. Cho KW, Morris DL, DelProposto JL, Geletka L, Zamarron B, Martinez-Santibanez G, et al. An MHC II-dependent activation loop between adipose tissue macrophages and CD4+ T cells controls obesity-induced inflammation. *Cell Rep.* 2014; 9:605–17. DOI: 10.1016/j.celrep.2014.09.004 [PubMed: 25310975]
79. Xiao L, Yang X, Lin Y, Li S, Jiang J, Qian S, et al. Large adipocytes function as antigen-presenting cells to activate CD4(+) T cells via upregulating MHCII in obesity. *Int J Obes (Lond).* 2016; 40:112–20. DOI: 10.1038/ijo.2015.145 [PubMed: 26248660]
80. Ioan-Facsinay A, Kwekkeboom JC, Westhoff S, Giera M, Rombouts Y, van Harmelen V, et al. Adipocyte-derived lipids modulate CD4+ T-cell function. *Eur J Immunol.* 2013; 43:1578–87. DOI: 10.1002/eji.201243096 [PubMed: 23504601]
81. Poloni A, Maurizi G, Ciarlantini M, Medici M, Mattiucci D, Mancini S, et al. Interaction between human mature adipocytes and lymphocytes induces T-cell proliferation. *Cytotherapy.* 2015; 17:1292–301. DOI: 10.1016/j.jcyt.2015.06.007 [PubMed: 26276010]
82. Arenaccio C, Anticoli S, Manfredi F, Chiozzini C, Olivetta E, Federico M. Latent HIV-1 is activated by exosomes from cells infected with either replication-competent or defective HIV-1. *Retrovirology.* 2015; 12:87.doi: 10.1186/s12977-015-0216-y [PubMed: 26502902]
83. Lazar I, Clement E, Dauvillier S, Milhas D, Ducoux-Petit M, LeGonidec S, et al. Adipocyte Exosomes Promote Melanoma Aggressiveness through Fatty Acid Oxidation: A Novel Mechanism Linking Obesity and Cancer. *Cancer Res.* 2016; 76:4051–7. DOI: 10.1158/0008-5472.CAN-16-0651 [PubMed: 27216185]
84. Zhang Y, Yu M, Tian W. Physiological and pathological impact of exosomes of adipose tissue. *Cell Prolif.* 2016; 49:3–13. DOI: 10.1111/cpr.12233 [PubMed: 26776755]
85. Barclay RA, Schwab A, DeMarino C, Akpamagbo Y, Lepene B, Kassaye S, et al. Exosomes from uninfected cells activate transcription of latent HIV-1. *J Biol Chem.* 2017; 292:14764.doi: 10.1074/jbc.A117.793521 [PubMed: 28887434]

86. Huang-Doran I, Zhang CY, Vidal-Puig A. Extracellular Vesicles: Novel Mediators of Cell Communication In Metabolic Disease. *Trends Endocrinol Metab.* 2017; 28:3–18. DOI: 10.1016/j.tem.2016.10.003 [PubMed: 27810172]
87. Hong X, Schouest B, Xu H. Effects of exosome on the activation of CD4+ T cells in rhesus macaques: a potential application for HIV latency reactivation. *Sci Rep.* 2017; 7:15611.doi: 10.1038/s41598-017-15961-x [PubMed: 29142313]
88. Shrivastav S, Kino T, Cunningham T, Ichijo T, Schubert U, Heinklein P, et al. 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. DOI: 10.1210/me.2007-0124 [PubMed: 17932108]
89. Levy DN, Refaeli Y, MacGregor RR, Weiner DB. Serum Vpr regulates productive infection and latency of human immunodeficiency virus type 1. *Proc Natl Acad Sci USA.* 1994; 91:10873–7. [PubMed: 7971975]
90. Romani B, Kamali Jamil R, Hamidi-Fard M, Rahimi P, Momen SB, Aghasadeghi MR, et al. HIV-1 Vpr reactivates latent HIV-1 provirus by inducing depletion of class I HDACs on chromatin. *Sci Rep.* 2016; 6:31924.doi: 10.1038/srep31924 [PubMed: 27550312]
91. Fletcher CV, Staskus K, Wietgreffe SW, Rothenberger M, Reilly C, Chipman JG, et al. Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. *Proc Natl Acad Sci USA.* 2014; 111:2307–12. DOI: 10.1073/pnas.1318249111 [PubMed: 24469825]
92. Janneh O, Hoggard PG, Tjia JF, Jones SP, Khoo SH, Maher B, et al. Intracellular disposition and metabolic effects of zidovudine, stavudine and four protease inhibitors in cultured adipocytes. *Antivir Ther.* 2003; 8:417–26. [PubMed: 14640389]
93. Vernochet C, Azoulay S, Duval D, Guedj R, Cottrez F, Vidal H, et al. Human immunodeficiency virus protease inhibitors accumulate into cultured human adipocytes and alter expression of adipocytokines. *J Biol Chem.* 2005; 280:2238–43. DOI: 10.1074/jbc.M408687200 [PubMed: 15525648]
94. Guallar JP, Cano-Soldado P, Aymerich I, Domingo JC, Alegre M, Domingo P, et al. Altered expression of nucleoside transporter genes (SLC28 and SLC29) in adipose tissue from HIV-1-infected patients. *Antivir Ther.* 2007; 12:853–63. [PubMed: 17926640]
95. Janneh O, Owen A, Bray PG, Back DJ, Pirmohamed M. The accumulation and metabolism of zidovudine in 3T3-F442A pre-adipocytes. *Br J Pharmacol.* 2010; 159:484–93. DOI: 10.1111/j.1476-5381.2009.00552.x [PubMed: 20015290]
96. Dankers AC, Sweep FC, Pertijs JC, Verweij V, van den Heuvel JJ, Koenderink JB, et al. Localization of breast cancer resistance protein (Bcrp) in endocrine organs and inhibition of its transport activity by steroid hormones. *Cell Tissue Res.* 2012; 349:551–63. DOI: 10.1007/s00441-012-1417-5 [PubMed: 22581381]
97. van Dijk A, Naaijken BA, Jurgens WJ, Oerlemans R, Scheffer GL, Kassies J, et al. The multidrug resistance protein breast cancer resistance protein (BCRP) protects adipose-derived stem cells against ischemic damage. *Cell Biol Toxicol.* 2012; 28:303–15. DOI: 10.1007/s10565-012-9225-y [PubMed: 22801743]
98. Francisco AF, Lewis MD, Jayawardhana S, Taylor MC, Chatelain E, Kelly JM. Limited Ability of Posaconazole To Cure both Acute and Chronic *Trypanosoma cruzi* Infections Revealed by Highly Sensitive In Vivo Imaging. *Antimicrob Agents Chemother.* 2015; 59:4653–61. DOI: 10.1128/AAC.00520-15 [PubMed: 26014936]
99. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, Inflammation, and Cancer. *Annu Rev Pathol.* 2016; 11:421–49. DOI: 10.1146/annurev-pathol-012615-044359 [PubMed: 27193454]
100. Himbert C, Delphan M, Scherer D, Bowers LW, Hursting S, Ulrich CM. Signals from the Adipose Microenvironment and the Obesity-Cancer Link-A Systematic Review. *Cancer Prev Res (Phila).* 2017; 10:494–506. DOI: 10.1158/1940-6207.CAPR-16-0322 [PubMed: 28864539]
101. Hoy AJ, Balaban S, Saunders DN. Adipocyte-Tumor Cell Metabolic Crosstalk in Breast Cancer. *Trends Mol Med.* 2017; 23:381–92. DOI: 10.1016/j.molmed.2017.02.009 [PubMed: 28330687]

102. Duong MN, Cleret A, Matera EL, Chettab K, Mathé D, Valsesia-Wittmann S, et al. Adipose cells promote resistance of breast cancer cells to trastuzumab-mediated antibody-dependent cellular cytotoxicity. *Breast Cancer Res.* 2015; 17:57.doi: 10.1186/s13058-015-0569-0 [PubMed: 25908175]
103. Sheng X, Tucci J, Parmentier JH, Ji L, Behan JW, Heisterkamp N, et al. Adipocytes cause leukemia cell resistance to daunorubicin via oxidative stress response. *Oncotarget.* 2016; 7:73147–59. DOI: 10.18632/oncotarget.12246 [PubMed: 27705905]
104. Sheng X, Parmentier JH, Tucci J, Pei H, Cortez-Toledo O, Dieli-Conwright CM, et al. Adipocytes Sequester and Metabolize the Chemotherapeutic Daunorubicin. *Mol Cancer Res.* 2017; In press. doi: 10.1158/1541-7786.MCR-17-0338
105. Cahu X, Calvo J, Poglio S, Prade N, Colsch B, Arcangeli ML, et al. Bone marrow sites differently imprint dormancy and chemoresistance to T-cell acute lymphoblastic leukemia. *Blood Adv.* 2017; 1:1760–72. DOI: 10.1182/bloodadvances.2017004960 [PubMed: 29296822]
106. Buck MD, O'Sullivan D, Pearce EL. T cell metabolism drives immunity. *J Exp Med.* 2015; 212:1345–60. DOI: 10.1084/jem.20151159 [PubMed: 26261266]
107. Norata GD, Caligiuri G, Chavakis T, Matarese G, Netea MG, Nicoletti A, et al. The Cellular and Molecular Basis of Translational Immunometabolism. *Immunity.* 2015; 43:421–34. DOI: 10.1016/j.immuni.2015.08.023 [PubMed: 26377896]
108. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol.* 2016; 16:553–65. DOI: 10.1038/nri.2016.70 [PubMed: 27396447]
109. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic Instruction of Immunity. *Cell.* 2017; 169:570–86. DOI: 10.1016/j.cell.2017.04.004 [PubMed: 28475890]
110. Gaber T, Strehl C, Buttgerit F. Metabolic regulation of inflammation. *Nat Rev Rheumatol.* 2017; 13:267–79. DOI: 10.1038/nrrheum.2017.37 [PubMed: 28331208]
111. Man K, Kutyavin VI, Chawla A. Tissue Immunometabolism: Development, Physiology, and Pathobiology. *Cell Metab.* 2017; 25:11–26. DOI: 10.1016/j.cmet.2016.08.016 [PubMed: 27693378]
112. Puleston DJ, Villa M, Pearce EL. Ancillary Activity: Beyond Core Metabolism in Immune Cells. *Cell Metab.* 2017; 26:131–41. DOI: 10.1016/j.cmet.2017.06.019 [PubMed: 28683280]
113. Shehata HM, Murphy AJ, Lee MKS, Gardiner CM, Crowe SM, Sanjabi S, et al. Sugar or Fat? Metabolic Requirements for Immunity to Viral Infections. *Front Immunol.* 2017; 8:1311.doi: 10.3389/fimmu.2017.01311 [PubMed: 29085369]
114. Hegedus A, Kavanagh Williamson M, Huthoff H. HIV-1 pathogenicity and virion production are dependent on the metabolic phenotype of activated CD4+ T cells. *Retrovirology.* 2014; 11:98.doi: 10.1186/s12977-014-0098-4 [PubMed: 25421745]
115. Palmer CS, Ostrowski M, Gouillou M, Tsai L, Yu D, Zhou J, et al. Increased glucose metabolic activity is associated with CD4+ T-cell activation and depletion during chronic HIV infection. *AIDS.* 2014; 28:297–309. DOI: 10.1097/QAD.000000000000128 [PubMed: 24335483]
116. Palmer CS, Ostrowski M, Balderson B, Christian N, Crowe SM. Glucose metabolism regulates T cell activation, differentiation, and functions. *Front Immunol.* 2015; 6:1.doi: 10.3389/fimmu.2015.00001 [PubMed: 25657648]
117. Palmer CS, Cherry CL, Sada-Ovalle I, Singh A, Crowe SM. Glucose Metabolism in T Cells and Monocytes: New Perspectives in HIV Pathogenesis. *EBioMedicine.* 2016; 6:31–41. DOI: 10.1016/j.ebiom.2016.02.012 [PubMed: 27211546]
118. Masson JJR, Murphy AJ, Lee MKS, Ostrowski M, Crowe SM, Palmer CS. Assessment of metabolic and mitochondrial dynamics in CD4+ and CD8+ T cells in virologically suppressed HIV-positive individuals on combination antiretroviral therapy. *PLoS One.* 2017; 12:e0183931.doi: 10.1371/journal.pone.0183931 [PubMed: 28854263]
119. Palmer CS, Duette GA, Wagner MCE, Henstridge DC, Saleh S, Pereira C, et al. Metabolically active CD4+ T cells expressing Glut1 and OX40 preferentially harbor HIV during in vitro infection. *FEBS Lett.* 2017; 591:3319–32. DOI: 10.1002/1873-3468.12843 [PubMed: 28892135]
120. Besnard E, Hakre S, Kampmann M, Lim HW, Hosmane NN, Martin A, et al. The mTOR Complex Controls HIV Latency. *Cell Host Microbe.* 2016; 20:785–97. DOI: 10.1016/j.chom.2016.11.001 [PubMed: 27978436]

121. Rasheed S, Yan JS, Lau A, Chan AS. HIV replication enhances production of free fatty acids, low density lipoproteins and many key proteins involved in lipid metabolism: a proteomics study. PLoS One. 2008; 3:e3003.doi: 10.1371/journal.pone.0003003 [PubMed: 18714345]
122. Angela M, Endo Y, Asou HK, Yamamoto T, Tumes DJ, Tokuyama H, et al. Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPAR γ directs early activation of T cells. Nat Commun. 2016; 7:13683.doi: 10.1038/ncomms13683 [PubMed: 27901044]
123. Simonetta F, Bourgeois C. CD4+FOXP3+ Regulatory T-Cell Subsets in Human Immunodeficiency Virus Infection. Front Immunol. 2013; 4:215.doi: 10.3389/fimmu.2013.00215 [PubMed: 23908654]
124. Chachage M, Pollakis G, Kuffour EO, Haase K, Bauer A, Nadai Y, et al. CD25+ FoxP3+ Memory CD4 T Cells Are Frequent Targets of HIV Infection In Vivo. J Virol. 2016; 90:8954–67. DOI: 10.1128/JVI.00612-16 [PubMed: 27384654]
125. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. Cell Metab. 2017; 25:1282–93e7. DOI: 10.1016/j.cmet.2016.12.018 [PubMed: 28416194]
126. Howie D, Cobbold SP, Adams E, Ten Bokum A, Necula AS, Zhang W, et al. Foxp3 drives oxidative phosphorylation and protection from lipotoxicity. JCI Insight. 2017; 2:e89160.doi: 10.1172/jci.insight.89160 [PubMed: 28194435]
127. Mansfield KG, Carville A, Wachtman L, Goldin BR, Yearley J, Li W, et al. A diet high in saturated fat and cholesterol accelerates simian immunodeficiency virus disease progression. J Infect Dis. 2007; 196:1202–10. DOI: 10.1086/521680 [PubMed: 17955439]

Table 1

Summary of evidence describing HIV/SIV reservoirs in adipose tissue

Reference	Study Subjects	AT Samples Studied	Main Virological Findings in AT	Main Immunological Findings in AT	Antiretroviral Distribution in AT
Koethe et al. 2017	HIV patients	SC	HIV DNA undetectable in SVF CD4 ⁺ s of most patients.	High CD57 ⁺ CD8 T cells. CD8/CD4 ratio >1. Distinct CD8 TCR repertoire compared to blood.	Not examined.
Hsu et al. 2017	SHIV-infected RM ⁺ s	SC, VS	SHIV RNA in AT of most RM ⁺ s.	Increased CD4 ⁺ s. Detectable Macs.	Not examined.
Damouche et al. 2017	HIV patients	SC, VS	Not examined.	PD1 ⁺ CD4 ⁺ s. Low activation phenotype of T cells.	Not examined.
Couturier et al. 2016	SIV/SHIV-infected RM ⁺ s	SC, VS	SHIV DNA in SVF of most RM ⁺ s. Infectious SIV in SVF CD4 ⁺ s of most RM ⁺ s.	Activated memory T cells, NK/NKT cells, Macs. CD8/CD4 >1.	Not examined.
Damouche et al. 2015	HIV patients, SIV-infected CM ⁺ s	SC, VS	SIV DNA/RNA in SVF CD4 ⁺ s of most RM ⁺ s. HIV DNA, RNA, and infectious HIV in SVF CD4 ⁺ s of most patients.	Activated memory T cells. Increased CD8/CD4 ratio. Increased inflammatory Macs.	Not examined.
Couturier et al. 2015	HIV patients	SC, VS	HIV DNA in SVF of most patients.	Activated memory T cells. CD8/CD4 >1.	Not examined.
Dupin et al. 2002	HIV patients	SC	HIV DNA undetectable in whole AT of most patients. RNA undetectable.	Not examined.	NNRTI detection in whole AT lysates. Minimal to undetectable NRTI ⁺ s and PI ⁺ s.

Abbreviations. AT; adipose tissue, CM; cynomolgus macaques, Macs; macrophages, NNRTI; non-nucleoside reverse transcriptase inhibitor, NRTI; nucleoside reverse transcriptase inhibitor, PI; protease inhibitor, SC; subcutaneous, RM; rhesus macaques, SVF; stromal-vascular-fraction, VS; visceral