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REVIEW ARTICLE

Obesity and Fat Metabolism in Human Immunodeficiency Virus–Infected Individuals: Immunopathogenic Mechanisms and Clinical Implications

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Metabolic complications relating to complex effects of viral and immune-mediated mechanisms are now a focus of clinical care among persons living with human immunodeficiency virus (PLHIV), and obesity is emerging as a critical problem. To address knowledge gaps, the US National Institutes of Health sponsored a symposium in May 2018 entitled "Obesity and Fat Metabolism in HIV-infected Individuals." Mechanisms relating to adipose dysfunction and fibrosis, immune function, inflammation, and gastrointestinal integrity were highlighted as contributors to obesity among PLHIV. Fibrotic subcutaneous adipose tissue is metabolically dysfunctional and loses its capacity to expand, leading to fat redistribution, including visceral obesity and ectopic fat accumulation, promoting insulin resistance. Viral proteins, including viral protein R and negative regulatory factor, have effects on adipogenic pathways and cellular metabolism in resident macrophages and T cells. HIV also affects immune cell trafficking into the adipose compartments, with effects on adipogenesis, lipolysis, and ectopic fat accumulation. Key cellular metabolic functions are likely to be affected in PLHIV by gut-derived cytokines and altered microbiota. There are limited strategies to reduce obesity specifically in PLHIV. Enhancing our understanding of critical pathogenic mechanisms will enable the development of novel therapeutics that may normalize adipose tissue function and distribution, reduce inflammation, and improve insulin sensitivity in PLHIV.

Keywords. HIV; obesity; viral proteins; inflammation; metabolism.

Obesity is emerging as a critical problem in people living with human immunodeficiency virus (PLHIV) in both resource-poor and resource-rich environments, with women more affected than men [1, 2] (Table 1). Obesity is associated with adipose tissue dysfunction in ways that promote insulin resistance and lipid abnormalities. Increased body mass index (BMI) is specifically associated with the development of cardiovascular disease, non-AIDS-related cancers, and type 2 diabetes in PLHIV [3]. Indeed, weight gain in PLHIV is more highly associated with these conditions than in the general population; every 5-pound gain is associated with a 14% increased risk for diabetes compared with only 8% in the general population [4]. With dramatic improvements in antiretroviral therapy (ART), noncommunicable diseases are now contributors to human immunodeficiency virus (HIV)–associated morbidity and mortality [3] and may in part be due to immune activation that persists despite effective HIV treatment. White adipose tissue (WAT) contains thermogenic adipocytes, often termed "beige," that are highly metabolically active and associated with leanness, as well as lipid-storing white adipocytes that are also critical metabolic regulators. Among individuals without HIV, obesity may contribute to a low-grade inflammatory state (metabolic inflammation), characterized by recruitment of immune cells into adipose tissue and secretion of adipocytokines. Among PLHIV, increased metabolic inflammation may significantly alter beige and white adipocyte function, producing critical health risks. Recognizing these converging factors, the National Institutes of Health sponsored a symposium in May 2018 entitled "Obesity and Fat Metabolism in HIV-Infected Individuals." This report describes selected topics discussed at that meeting highlighting the biological basis of obesity in HIV.

ADIPOSE TISSUE FIBROSIS AND ECTOPIC VISCERAL ADIPOSE TISSUE IN HIV

Obesity is characterized by expansion of both subcutaneous and intra-abdominal (visceral) fat (Figure 1). However, insulin resistance and increased cardiometabolic risk are associated

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Table 1. Reported Prevalence of Obesity in People With Human Immunodeficiency Virus, by Region

Author (Year)	Country	Population	No.	Male, No. (%)	Age[a]	ART, No. (%)	Obesity, No. (%)	Overweight, No. (%)
Africa								
WHO region estimate, %	…	…	…	…	…	…	10.6%	27.7%
Semu et al (2016)	Tanzania	PLHIV enrolled in care	53 825	16 685 (31)	35	6503 (12)	3840 (7.1)	9890 (18.3)
Julius et al (2011)	South Africa	HIV outpatient clinic	304	67 (22)	>35	…	51 (16.8)	88 (29.0)
Ezechi et al (2016)	Nigeria	Cohort study	8819	3157 (35.8)	35.5	…	668 (7.4)	1664 (19.7)
							2337 (26.5)[b]	3148 (35.7)[b]
Muyanja et al (2016)	Uganda	PLHIV on nonnucleoside ART	250	80 (32)	36	250 (100)	30 (12)	57 (22.8)
Guehi et al (2016)	Cote d'Ivoire	Temprano Trial	597	150 (25)	36	597 (100)	55 (9.2)[c]	148 (24.8)[c]
Malaza et al (2012)	South Africa	Population-based survey	1945	…	…	369 (19)	390 (20)	504 (26)
Europe								
WHO region estimate, %	…	…	…	…	…	…	23.3%	62.3%
Obry-Roguet et al (2018)	France	HIV outpatient clinic	862	585 (67.9)	51.2	787 (91)	46 (5.3)	191 (22.2)
Pourcher et al (2015)	France	French Hospital Database on HIV	37 505	25 128 (67)	>40	32 629 (87)	3169 (8.4)	12 701 (33.8)
Ilozue et al (2017)	England	PLHIV in outpatient care	560	385 (68.8)	45	507 (90.5)	145 (25.8)	217 (38.7)
North America								
WHO US estimate, %	…	…	…	…	…	…	36.2%	70.2%
Thompson-Paul et al (2015)	US	PLHIV in outpatient care	4006	2941 (73.2)	>40	3366 (84)	1023 (25.5)	…
Arbeitman et al (2014)	US	Youth with perinatally acquired HIV	134	64 (48)	16.5	120 (90)	30 (22)	18 (13.4)
Blashill et al (2013)	US	MSM with HIV (CNICS)	864	864 (100)	44	864 (100)	107 (12)	363 (42)
Messina et al (2014)	Canada	HIV outpatient clinic	886	797 (90)	47	788 (89)	116 (14)	294 (34)
Taylor et al (2014)	US	South Texas HIV Cohort	1214	968 (79.7)	42	1170 (96.4)	268 (22.1)	455 (37.5)
Koethe et al (2016)	US/Canada	Nationwide cohort (NA-ACCORD)	14 084	11 690 (83)	40	0 (0)	2096 (14.8)	4275 (30.3)
Crum-Cianflone et al (2010)	US	US Military natural history study	1682	1564 (93)	31	0 (0)	157 (9.3)	623 (37)
Crum-Cianflone et al (2008)	US	US Military	661	661 (100)	41	479 (72.5)	112 (17)	304 (46)
Boodram et al (2009)	US	Prospective cohort study (WHIS)	2157	0 (0)	36	1304 (60)	240 (33)	205 (28)
Becofsky et al (2016)	US	HIV outpatient clinic/hospital	1489	1047 (70)	48	1241 (85.2)	420 (28.8)	553 (37.9)
South America								
WHO Brazilian estimate, %	…	…	…	…	…	…	22.1%	56.9%
Bakal et al (2018)	Brazil	HIV outpatient clinic	1794	1100 (61.3)	36	0 (0)	141 (7.9)	390 (22)
Kroll et al (2012)	Brazil	HIV outpatient clinic	354	203 (57.3)	43	268 (75.9)	30 (8.4)	121 (34.2)

Results extrapolated from data stratified by subgroups or presented only as percentages where necessary. Obesity defined as body mass index (BMI) ≥30 kg/m^2 and overweight as BMI 25–29.9 kg/m^2. WHO estimates drawn from the Global Health Observatory (2017); available at: http://apps.who.int/gho/data/node.main.A896?lang=en.

References: Arbeitman et al (J Pediatr Gastroenterol Nutr. **2014**;59:449–54); Bakal et al (J Antimicrob Chemother. **2018**;73:2177–85); Becofsky et al (Obes Sci Pract. **2016**;2:123–7); Blashill et al (J Int Assoc Provid AIDS Care. **2013**;12:319–24); Boodram et al (AIDS Patient Care STDS. **2009**;23:1009–16); Crum-Cianflone et al (PLoS One. **2010**;5:e10106); Crum-Cianflone et al (AIDS Patient Care STDS. **2008**;22:925–30); Ezechi et al (Ceylon Med J. **2016**;61:56–62); Guehi et al (AIDS Res Ther. **2016**;13:12); Ilozue et al (Int J STD AIDS. **2017**;28:284–9); Julius et al (Curr HIV Res. **2011**;9:247–52); Koethe et al (AIDS Res Hum Retroviruses. **2016**;32:50–8); Kroll et al (Arq Bras Endocrinol Metabol. **2012**;56:137–41); Malaza et al (PLoS One. **2012**;7:e47761); Messina et al (J Assoc Nurses AIDS Care. **2014**;25:652–6); Muyanja et al (AIDS Patient Care STDS. **2016**;30:4–10); Obry-Roguet et al (Medicine (Baltimore). **2018**;97:e10956); Pourcher et al (J Visc Surg. **2015**;152:33–7); Semu et al (J Int Assoc Provid AIDS Care. **2016**;15:512–21); Taylor et al (J Acquir Immune Defic Syndr. **2014**;65:e33–40); Thompson-Paul et al (Medicine (Baltimore). **2015**;94:e1081).

Abbreviations: ART, antiretroviral therapy; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HIV, human immunodeficiency virus; MSM, men who have sex with men; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; PLHIV, people living with HIV; US, United States; WHIS, Women's Interagency HIV Study; WHO, World Health Organization.

[a]Mean or median as reported, or >*x* years when ≥50% of population was reported to be over that age.

[b]Obesity/overweight prevalences following 5 years of ART.

[c]Prevalence at 24-month follow-up visit for the participants randomized to immediate ART.

with WAT inflammation and reduced thermogenesis, changes that are closely linked to visceral obesity [5]. Therefore, efforts are ongoing to identify what drives visceral fat expansion. Data also show that WAT fibrosis is associated with insulin resistance and diabetes [6–8]. Specifically, recent work shows that people with subcutaneous WAT (scWAT) fibrosis have more fibroadipogenic precursors in the scWAT that express platelet-derived growth factor receptors and CD9/Tetraspanin27 and that differentiate into adipocytes capable of producing collagen and promoting extracellular matrix deposition [9].

Healthy scWAT shrinks as it releases fatty acids to the body during fasting or starvation. However, it has the capacity

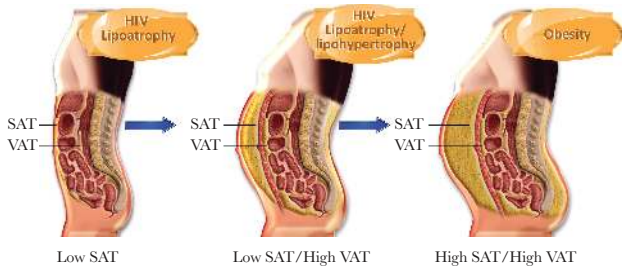

Figure 1. Spectrum of body composition changes past, present, and future in human immunodeficiency virus (HIV). Fat dysfunction in HIV related to loss of subcutaneous adipose tissue (SAT) or lipoatrophy, gain of visceral adipose tissue (VAT) or lipohypertrophy, and gain of SAT and VAT in obesity.

to rapidly reexpand when food intake resumes. scWAT fibrosis limits this dynamic plasticity, essential for metabolic adaptability. In the current obesogenic food environment, fibrosis can limit scWAT expansion and promote fat deposition in other depots, including the visceral WAT (vWAT). The role of scWAT fibrosis in promoting insulin resistance is supported by both mouse models and human studies, including ethnic comparisons across a wide range of visceral adiposity [10–14]. Although some observational studies suggest that PLHIV develop more scWAT fibrosis than uninfected people, especially in the context of lipodystrophy [15], it is unknown whether fibrosis drives insulin resistance in this setting.

The vWAT expands when the capacity for scWAT expansion is exceeded [16, 17]. Lipids may then infiltrate the liver and other nonadipose organs with clinical consequences. Imaging studies link such ectopic fat deposition to insulin resistance and cardiometabolic disease. Epicardial and perivascular fat, for example, are increased in those with chronic HIV, and expansion of each is implicated in heightened cardiometabolic risk [18].

REGULATION OF ADIPOGENESIS BY HIV

HIV produces accessory proteins that control replication and influence adipocyte and T-cell metabolism. The most comprehensively studied viral proteins are viral protein R (Vpr) and negative regulatory factor (Nef). Vpr circulates in the blood even in those with undetectable viral loads [19]. In animal models, with transgenic overexpression or systemic infusion, Vpr blocks preadipocyte differentiation and peroxisome proliferator–activated receptor gamma (PPAR-γ) expression, while simultaneously stimulating the glucocorticoid receptor in adipocytes and inhibiting PPAR-γ in hepatocytes [20], resulting in increased lipolysis, hyperglycemia, hypertriglyceridemia, and hepatic steatosis [20].

The viral accessory proteins may also regulate metabolism by controlling gene transcription via Dicer, a cytoplasmic type III RNAse that cleaves pre-microRNAs into mature microRNAs. HIV reduces Dicer and enhances infectivity by altering microRNA expression important to host defenses. Simultaneously, reduction of Dicer by HIV accessory proteins may reduce microRNAs that maintain adipose differentiation. Animal knockout models of Dicer demonstrate lipodystrophy; loss of scWAT, including metabolically favorable beige cells; adipocyte senescence; and increased dorsocervical fat [22]. These changes are associated with insulin resistance [22], similar to PLHIV. Among PLHIV, particularly those with lipodystrophy, marked by clinical evidence of dorsocervical fullness and lipohypertrophy, there is reduced Dicer expression in the scWAT when compared to age-matched controls (Figure 2). Reduced Dicer expression is also associated with lower levels of thermogenic fat markers in HIV, suggesting a linkage of the virus, through Dicer, to dysfunctional adipose tissue [23]. Among PLHIV, reduced Dicer expression and abdominal subcutaneous adipose tissue dysfunction are associated with increased dorsocervical fat [23]. Increased dorsocervical fat in HIV is characterized by increased DIO2, a deiodinase that contributes to thermogenesis in beige fat, as well as increased energy expenditure [24]. Dorsocervical fat accumulation may therefore increase to compensate for generalized subcutaneous adipose dysfunction. Taken together, these data suggest that HIV and its related proteins may potentially affect critical adipogenic pathways controlling energy expenditure and lipid metabolism contributing to metabolic dysfunction. Further studies are needed to assess these affects among those achieving

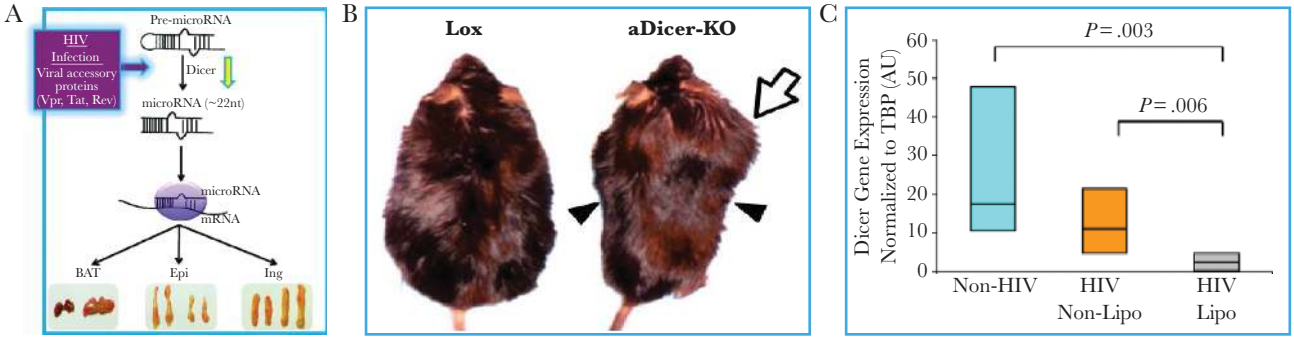

Figure 2. Human immunodeficiency virus (HIV)/viral protein effects on adipose-specific Dicer, and implications of Dicer expression to lipodystrophy in preclinical and human models. *A*, Potential mechanism of HIV and viral accessory protein–mediated suppression of Dicer leading to microRNA dysregulation and fat dysfunction in brown adipose tissue and the epididymal and inguinal adipose depots [21]. *B*, Adipose-specific knockout mice demonstrate a lipodystrophy phenotype compared to control mice. Arrow depicts dorsocervical fullness and arrowheads depict loss of subcutaneous adipose tissue [22]; *C*, Significant reduction in Dicer expression in abdominal subcutaneous adipose tissue, with a stepwise decrease in expression demonstrated to be highest among non-HIV-infected individuals and most reduced among HIV-infected individuals with lipodystrophy [23]. Figures adapted and used with permission [21–23]. Abbreviations: AU, arbitrary units; BAT, brown adipose tissue; Epi, epididymal; HIV, human immunodeficiency virus; Ing, inguinal; KO, knockout; Lipo, lipodystrophy; mRNA, messenger RNA; TBP, TATA-box binding protein; Vpr, viral protein R.

virological suppression with undetectable virus and low circulating concentrations of accessory proteins.

IMMUNOLOGICAL PHENOTYPE OF ADIPOSE TISSUE: RESIDENT T CELLS AND MACROPHAGES

WAT represents a complex immunologic environment comprised of cells of the adaptive and innate lineages, which serve to identify and eliminate a range of infiltrating viruses and other pathogens, with subsequent effects on adipocyte regulation and energy storage and release. A central feature of the WAT immunologic milieu in HIV, and in simian immunodeficiency virus (SIV) infections in macaques, is a profound shift in WAT T-cell profile toward a $CD8^+$ T-cell predominance [25–27]. WAT T cells in PLHIV primarily have a $CD45RO^+$ memory phenotype with high levels of CD69 expression, an inducible early-activation indicator [28], and have high expression of CD57 on $CD8^+$ T cells, a marker of late differentiation and senescence and reduced replicative capacity [29, 30].

The finding that WAT from lean PLHIV and SIV-infected macaques is enriched for $CD8^+$ T cells is intriguing as similar changes are a hallmark of obesity. Obese HIV-negative individuals have increased adipose tissue $CD8^+$ T cells, $CD4^+$ Th1 cells, and Th17 cells; fewer Treg cells; and an increase in M1-phenotype ($CD68^+$, tumor necrosis factor [TNF] α, interleukin [IL] 12, and IL-23–producing) proinflammatory macrophages [31–34]. In mice, progressive obesity is also accompanied by increased WAT T-cell clonality [35–37]. Furthermore, WAT $CD8^+$ T-cell infiltration is an early and necessary factor for the recruitment of TNF-α, IL-6, and IL-12–producing macrophages in obesity [31]. IL-6, TNF-α, and other cytokines exert their effects via adipocyte surface receptors and other mechanisms to impair insulin signaling through reduced expression of insulin receptor substrate 1, phosphoinositide 3-kinase (PI3K) p85α, and glucose transporter (Glut) type 4 [38, 39] as discussed below.

While WAT in HIV and SIV infection is characterized by a marked increase in $CD8^+$ T cells, the changes in $CD4^+$ T-cell subsets are less pronounced. WAT $CD4^+$ T cells harboring latent HIV likely contribute to local inflammation. Co-culture of preadipocytes with $CD4^+$ T cells containing proviral DNA increases preadipocyte IL-6 expression nearly 3-fold [25]. Release of viral proteins (Vpr or Tat) from infected cells has direct effects on cytokine production [19, 40, 41]. Compared to HIV-uninfected persons with similar BMI, scWAT in PLHIV has a significantly higher proportion of CD4 regulatory T cells (Tregs) identified by cell surface expression of CD25, as well as the transcription factor Foxp3, which could confer a beneficial anti-inflammatory effect. In contrast, there are no major differences in Th1 and Th17 proinflammatory subsets [26] between the 2 groups. However, there are fewer WAT Tregs in obesity, and loss of these cells may facilitate an influx of proinflammatory T cells and macrophages [32]. Thus, both HIV-specific factors as well as metabolic dysfunction related to obesity may contribute to the degree of tissue inflammation among obese PLHIV.

CELLULAR METABOLISM IN MACROPHAGE INFLAMMATORY RESPONSES IN ADIPOSE TISSUE

The metabolic state of immune cells is linked to their immune cell functions and to inflammatory processes. Immune cell metabolism is altered by HIV viral products. Glucose is metabolized via 2 major pathways: oxidative phosphorylation in the mitochondria producing maximal adenosine triphosphate (ATP), and glycolysis in the cytosol producing less ATP. The key event that marks metabolic reprogramming of lipopolysaccharide (LPS)–stimulated monocytes and macrophages is the overexpression of Glut1, the major glucose transporter that supports an increase in glycolytic influx and a proinflammatory phenotype (Figure 3). LPS-mediated signaling in macrophages initiates a metabolic switch from oxidative phosphorylation to glycolysis [42], producing metabolites necessary for growth and inflammatory responses. In a mouse model, blocking oxidative metabolism increases the number of proinflammatory M1 macrophages [43], and LPS-activated monocytes have increased glycolysis [44]. Glut1, a surrogate indicator of glycolysis, is increased on inflammatory monocytes in PLHIV, regardless of treatment status, and is considered a marker of immune activation and inflammation [44].

In murine models of obesity, WAT macrophages adipose tissue macrophages (ATMs) exhibit high glucose metabolic activity with elevated surface Glut1, and secrete high amounts of proinflammatory cytokines. This link between inflammation and metabolism supports the observed predominance of "metabolically activated" M1-like ATMs in the WAT of obese individuals relative to the anti-inflammatory M2 ATMs, which are more abundant in lean individuals. M2 macrophages are reliant on fatty acid oxidation and oxidative phosphorylation [45]; in the context of HIV infection, metabolic reprogramming of monocytes and macrophages is driven from an oxidative phenotype toward a proinflammatory glycolytic state [46]. A greater understanding of ATM metabolism may provide new therapeutic targets relevant to HIV-related comorbidities.

The metabolic programming during immune cell activation is coordinated in part by the PI3K/Akt/mechanistic target of rapamycin (mTOR) axis that posttranslationally regulates Glut1 trafficking to the cell membrane [47]. Normalization of overactive metabolic activity in both blood monocytes and ATM by therapeutic targeting of these pathways presents potential ways to alleviate the combinatorial effects of obesity and HIV. In animal models of obesity, PI3K inhibitors such as CNIO-PI3Ki and GDC-0941 decreased serum glucose levels without toxic effects [48]. Furthermore, mTOR inhibitors such as rapamycin dampen inflammatory responses by reducing inflammatory cytokine production by macrophages [49, 50] Taken together,

metabolic targeting of immune cells represents a new therapeutic approach to treat metabolic and chronic inflammatory diseases.

It remains to be determined whether HIV itself induces metabolic shifts in immune cells within the adipose environment, but several lines of reasoning point to the possibility. Glut1 is elevated on peripheral monocytes and CD4$^+$ T cells in PLHIV, including those on suppressive ART [51], and these cells may be recruited to the arterial endothelium and the adipose tissue (Figure 3). Vpr can increase mTOR activity in CD4$^+$ T cells, which controls cellular metabolism, HIV replication, and latency. This metabolic programming of immune cells initiates a vicious inflammatory cycle where HIV and obesity play important synergistic roles.

IMMUNOMODULATORY EFFECTS OF ADIPOKINES

Adipokines, hormones produced by adipocytes, have metabolic, neuroendocrine, and immunomodulatory effects. Leptin, a regulator of appetite via hypothalamic receptors, also has immunoregulatory effects. In in vitro studies, leptin promotes proinflammatory cytokine expression by macrophages and monocytes and acts directly on hepatocytes to promote C-reactive protein expression. Mature CD4$^+$ T cells express the long isoform of the leptin receptor [52] through which leptin signals provoke proliferative responses and induce activation in antigen-primed T cells and polarizes CD4$^+$ T cells toward a Th1 phenotype [52–57]. Leptin also increases monocyte, macrophage, and dendritic cell expression of anti-inflammatory cytokines (eg, IL-10 and IL-1 receptor antagonist) and suppresses interferon-γ in LPS-stimulated human macrophages [58, 59]. The administration of physiologic quantities of recombinant leptin to HIV-negative adults with acquired or congenital lipodystrophy confers higher circulating CD4$^+$ and CD8$^+$ T-cell counts, but 2 small trials in PLHIV with lipodystrophy on ART did not show an increase in CD4$^+$ T cells.

Another adipokine, adiponectin, has insulin-sensitizing effects on several metabolically active tissues, and circulating levels decline in obesity and in PLHIV [60]. Adiponectin exerts anti-inflammatory effects by inhibiting macrophage differentiation and production of TNF-α, reducing adipose tissue endothelial adhesion molecule expression, stimulating the production of IL-10 and IL-1 receptor antagonists, and reducing T-cell proliferation. T cells treated with adiponectin show reduced expansion after antigen stimulation, increased apoptosis, and reduced cytokine production [61]. Total and high-molecular-weight adiponectin have been shown to improve the anti–hepatitis C–specific T-cell responses, suggesting a favorable role in viral immunity [62].

INTERCELLULAR MEDIATORS: SEX HORMONES

The interaction between sex hormones and immune cells may impact adipose dysfunction in HIV. Estrogen and testosterone have a critical influence on adipose tissue phenotype in the non-HIV population. Hypogonadal states are associated with abdominal fat accumulation and metabolic dysregulation. Sex steroid deprivation among non-HIV-infected men correlates with increases in adipose tissue T cells and macrophage populations [63] with stronger associations of testosterone to T cells and estrogen to macrophages. Lower estrogen and testosterone levels have been demonstrated among men with HIV and lipodystrophy compared to those without lipodystrophy [64]. Estrogen has differential binding capacity to estrogen receptors in the subcutaneous vs visceral depot based on sex and may affect lipolysis through its actions on the estrogen receptor [65]. Emerging data suggest that overexpression of the protein prohibitin in the adipose depot may confer an obese phenotype that is sex neutral. However, the same protein may induce metabolic dysregulation in a sex-dimorphic pattern via cross-talk with sex steroids and immune signaling. Mechanistic investigation of prohibitin may yield further insight into linking sex-specific differences in fat redistribution, chronic low-grade inflammation, and metabolic complications among PLHIV.

GASTROINTESTINAL TRACT BARRIER BREAKDOWN, DYSBIOSIS, AND ADIPOCYTE INFLAMMATION

The gastrointestinal tract may play an important role in obesity, adipose tissue inflammation, and metabolic disorders (Figure 4).

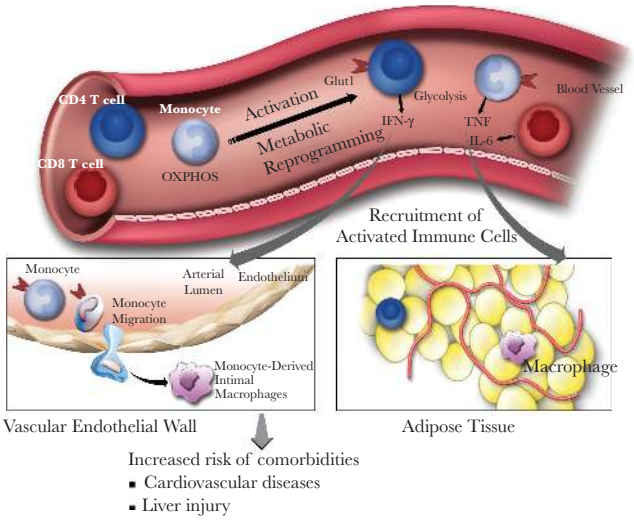

Figure 3. Model of how immune cell metabolic programming in human immunodeficiency virus (HIV) infection drives inflammation and may promote comorbidities. Inactivated T cells and monocytes utilize oxidative phosphorylation to generate adenosine triphosphate from fatty acids and limited glucose. During activation, cells undergo metabolic reprogramming toward a proinflammatory glycolytic profile by increasing surface glucose transporter 1 to increase glucose uptake. Metabolically activated monocytes may be recruited to arterial endothelium where they bind and migrate to the intima, differentiate into macrophages, and perpetuate atherosclerosis. Likewise, activated peripheral immune cells may be recruited to adipose tissue to orchestrate an inflammatory environment. Abbreviations: Glut 1, glucose transporter 1; IFN-γ, interferon gamma; IL-6, interleukin 6; OXPHOS, oxidative phosphorylation; TNF, tumor necrosis factor.

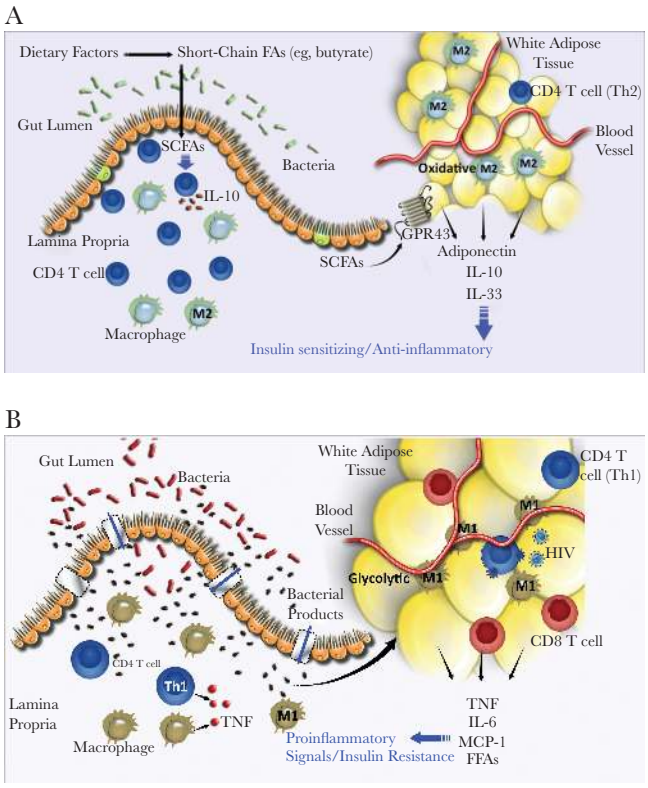

Figure 4. *A,* Gut and white adipose tissue homeostasis in human immunodeficiency virus (HIV)–uninfected lean individuals. Commensal bacteria and microbial products such as lipopolysaccharide (LPS) are restricted to the gut lumen by an intact mucosal barrier. Short-chain fatty acids (SCFAs) produced by "good" bacteria, eg, firmicutes, from the metabolism of complex fibers produce SCFAs such as butyrate, which maintain gut integrity and production of anti-inflammatory cytokines by immune cells within the lamina propria. SCFAs also regulate GPR43 on adipocytes to suppress lipid accumulation. In lean white adipose tissue, Th2 lymphocyte and M2 macrophages predominate, and anti-inflammatory cytokines and insulin-sensitizing adipokines are released. *B,* Model of gut and white adipose tissue homeostasis in obese people living with HIV (PLHIV). HIV causes a breach of intestinal epithelial barrier due to loss of tight junctions. Translocation of commensal bacteria and bacterial products including LPS and metabolites from the gut lumen into the lamina propria ensues. HIV infection depletes lamina propria $CD4^+$ T cells and, combined with a compromised gut barrier, induces potent proinflammatory gut response. Translocation of microbial products into white adipose tissue and peripheral blood causes systemic and white adipose inflammation that may promote or exacerbate obesity and creates a vicious cycle. In PLHIV, a disordered gut microbiome, characterized by reduced bacterial diversity and a shift from Firmicutes dominating phyla to pathobionts such as Proteobacteria and Bacteroidetes has been described. SCFAs such as propionate and acetate are produced, which have important immunological activity only now being elucidated. Metabolically activated and inflammatory immune cells within obese white adipose tissue secrete chemokines and proinflammatory cytokines, and enlarged adipocytes secrete free fatty acids and adipokines that induce insulin resistance. Activated resident $CD4^+$ T cells and macrophages within adipose tissues are also targets and reservoirs for HIV. Abbreviations: FA, fatty acid; FFA, free fatty acid; HIV, human immunodeficiency virus; IL, interleukin; MCP-1, Monocyte chemoattractant protein 1; SCFA, short-chain fatty acid; TNF, tumor necrosis factor.

Microbial translocation due to loss of mucosal integrity is a critical driver of adipose tissue inflammation in PLHIV. The intestinal wall is altered early in HIV infection and the alterations persist despite ART. These changes include villous atrophy, apoptosis of enterocytes, loss of tight junctions, abnormal B-cell function, decreased immunoglobulin A production, and depletion of $CD4^+$ T cells, especially Th17 cells [14]. Both HIV and obesity are associated with increased intestinal permeability to bacterial LPS. In animal models, LPS triggers gains in visceral adipose tissue and adipose tissue inflammation mediated via LPS's coreceptor, CD14 [66]. Obesity and HIV are both associated with a disordered intestinal microbiome characterized by a loss of gut microbial diversity and a deleterious metabolome [67]. It is postulated that short-chain fatty acids such as propionate and acetate are directed to regulate lipogenesis and gluconeogenesis in the liver, whereas butyrate, a metabolic product of bacterial digestion of complex carbohydrates, is an important energy source for colonic epithelial cells. These moieties are increasingly recognized as both immunologically and metabolically active and they may have epigenetic effects [68–71]. Their significance in HIV is an active area of research [69–73].

PREDICTORS OF CLINICAL OUTCOMES

Body mass index (kg/m^2) is an indirect estimate of body fat based on height and weight and is used to identify obesity [74]. Because adipose tissue preferentially accumulates in visceral organs, and lean body mass is reduced in chronic HIV, BMI may not be an accurate reflection of adiposity-related risk in PLHIV. A measurement of central obesity, or an evaluation of body composition, may better evaluate risk. Waist circumference and calculations that correct for height are not dependent on age, sex, or ethnicity, may be better predictors of cardiometabolic risk than BMI [75]. While body fat composition can be quantified with advanced imaging techniques, such as computed tomography or dual-energy x-ray absorptiometry, they are impractical in most clinical settings. Waist and hip measurements are simple, noninvasive, and inexpensive, and provide a good estimate of central obesity. Surrogate markers, such as serum levels of soluble CD14, and anthropometric measurements (eg, low thigh mass), have predictive values for comorbid risk in PLHIV, but may not add significant value in a heterogenous population or low-resource settings. For example, while soluble CD163 and serum levels of adipokines were significantly associated with liver fibrosis in PLHIV, obesity remained the strongest predictor of liver fibrosis in multivariable analyses [76].

METABOLIC CONSEQUENCES OF ART

Clinical trials have assessed the role of ART in the development of obesity. Overall, no convincing differential effect of the nucleoside reverse transcriptase inhibitor or nonnucleoside reverse transcriptase inhibitor (NNRTI) classes has been observed, although recent observational data point to a potential for higher weight gain with tenofovir alafenamide. The role of protease inhibitors (PIs) remains uncertain. While PIs do not generally lead to more total or central obesity than NNRTIs, ritonavir-boosted atazanavir may be an exception with a trend toward

greater gains in central fat observed when compared to NNRTIs and older PIs [77, 78]. However, ritonavir-boosted atazanavir and darunavir had similar effects on visceral adiposity in 2 other studies [79, 80].

Emerging data suggest that integrase inhibitors are associated with increased weight gain. In randomized studies, raltegravir led to similar visceral adipose tissue accumulation when compared to PIs [79], but was associated with larger gains in waist circumference and a higher incidence of severe weight gain through 96 weeks of ART [81, 82]. Observational and cohort studies suggest that integrase inhibitors can lead to excessive gains in body weight, dolutegravir and raltegravir more than elvitegravir [83–86]. In cell culture, elvitegravir has been found to inhibit adipocyte differentiation and the expression of genes controlling adipogenesis. ART clearly interacts with several other factors, including female sex, race, and gut integrity [79, 82, 87] and potentiates the effect of consumption of a high-fat diet on obesity in PLHIV [88].

TREATMENT STRATEGIES FOR THE MANAGEMENT OF OBESITY AND METABOLIC COMPLICATIONS

Treatments for obesity in HIV may include those used in the general population, as well as more tailored therapeutic strategies (Figure 5). Several groups have studied the treatment of obesity in PLHIV with mixed success. The first randomized trial testing an internet based behavioral weight loss program for PLHIV demonstrated a 4.4 kg average weight loss. However, there was significant variability in outcomes and only 30% of the patients achieved a 5% weight loss in the 12-week study [89]. While diet-induced weight loss improved insulin sensitivity in women with HIV to the same extent as HIV-negative women, weight loss caused a greater decline in fat-free mass in PLHIV. This suggests that the best modalities for weight loss in PLHIV should combine diet with both aerobic exercise and resistance exercise training to preserve fat-free mass. Due to the paucity of evidence, current obesity treatment guidelines for PLHIV [90] do not indicate specific exercise considerations. Recommendations include dietary modifications, both aerobic and resistance exercise training, antiobesity medications, and bariatric surgery when appropriate.

Recent studies have taken advantage of knowledge regarding hormone-mediated physiology to test novel pharmaceutical approaches to fat reduction, related inflammation, and metabolic dysfunction in HIV. In PLHIV, metformin leads to improvements in body weight, waist circumference, and insulin resistance, and prevents the progression of coronary calcium [91, 92]. PLHIV with excess visceral adiposity demonstrate increased renin-angiotensin-aldosterone system activation [93]. Initial studies show that eplerenone, a mineralocorticoid receptor blocker, may have beneficial effects on inflammation, lipids, and ectopic fat depots [94], and telmisartan (a combination angiotensin receptor antagonist and PPAR-γ agonist)

Figure 5. Selected interventions for managing obesity. Asterisks (*) indicate those strategies that are literature-based for treatment of human immunodeficiency virus (HIV) obesity as well as obesity without HIV. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; DASH, Dietary Approaches to Stop Hypertension; DPP-4, Dipeptidyl peptidase-4; GLP-1, Glucagon-like peptide-1; PPAR-γ, peroxisome proliferator–activated receptor gamma.

may modestly reduce adiposity in PLHIV [95]. Tesamorelin, a growth hormone–releasing hormone analogue, is US Food and Drug Administration (FDA) approved to reduce visceral adiposity in PLHIV, increases lean mass and is neutral to weight. Another adipose-targeted strategy includes the GLP-1 receptor agonists; liraglutide, FDA approved for obesity management in the non-HIV population, is associated with a mean weight loss of 4–8 kg over 56 weeks [96, 97]. In HIV, sitagliptin, a DPP-4 inhibitor, may have local anti-inflammatory effects on the adipose depot [98]. Detailed studies are needed to assess the benefit of GLP-1 receptor agonists on fat reduction in PLHIV. Medical therapies with dual action to reduce inflammation and adiposity are particularly attractive. Exploratory studies with probiotics/prebiotics such as *Lactobacillus gasseri* strains/galactomannan suggest potential effects in obesity trials [99], perhaps due to effects on short-chain fatty acids. Further studies among PLHIV are necessary before any firm conclusions can be drawn as to clinical utility of these moieties in weight management.

CONCLUSIONS

Understanding the contributions of HIV and its related proteins to the immunopathogenesis of obesity and related inflammatory and metabolic complications is a critical priority for PLHIV. Although our understanding of the mechanisms and strategies to combat obesity in HIV is increasing, significant controversies and unknowns remain. A stepwise targeted approach is

necessary to evaluate specific molecular mechanisms by which HIV regulates adipogenesis, fibrosis, immune cellular metabolism, and gut integrity and the exact contribution of ongoing or intermittent viral replication. This research may have important implications for understanding the mechanisms of adipose-related mechanisms of inflammation that drive cardiometabolic and noncommunicable disease risk in HIV and may elucidate novel mechanisms regulating these pathways in the general population. Such research will allow us to develop tailored therapeutic strategies to combat the growing epidemic of obesity among PLHIV.

Notes

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