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Dysfunctional Immunometabolism in HIV Infection: Contributing Factors and Implications for Age-related Comorbid Diseases.

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Abstract

Purpose of Review.—An increasing body of evidence indicates that persons living with HIV (PLWH) display dysfunctional immunometabolism. Here we provide an updated review of this topic and its relationship to HIV-associated immune stimuli and age-related disease.

Recent Findings.—HIV infection alters immunometabolism by increasing reliance on aerobic glycolysis for energy and productive infection and repurposing oxidative phosphorylation machinery for immune cell proliferation and survival. Recent studies in PLWH with diabetes mellitus and cardiovascular disease have identified an association with elevated T cell and monocyte glucose metabolism, respectively. Immunometabolic dysfunction has also been observed in PLWH in frailty and additional studies suggest a role for immunometabolism in non-AIDS defining cancers and neurocognitive disease. There is a plethora of HIV-associated immune stimuli that could drive immunometabolic dysfunction and age-related disease in PLWH but studies directly examining their relationship are lacking.

Summary.—Immunometabolic dysfunction is characteristic of HIV infection and is a potential link between HIV-associated stimuli and age-related comorbidities.

Keywords

HIV; Antiretroviral Therapy; Immune Activation; Immunometabolism; Glycolysis; Oxidative Phosphorylation

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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Introduction

Immune activation and inflammation are fundamental components in the pathogenesis of HIV infection that persists in antiretroviral therapy (ART)-treated people living with HIV (PLWH), even those receiving ART treatment during acute infection [1–4]. Non-AIDS comorbidities that typically manifest with advancing age have become increasingly common in the ART era [5,6], with many of these comorbidities showing associations with immune activation [7,8]. The drivers of immune activation are likely multifactorial and even with the advent of a sterilizing or functional cure could persist, as exemplified by elite controllers that display elevated immune activation compared to healthy controls [9].

Unlike most other cells within the body, many types of immune cells demonstrate the ability to switch their metabolic program when activated to generate energy and synthesize the machinery needed to achieve efficient immune function [10]. Key metabolic pathways implicated include glycolysis, glutaminolysis, fatty acid oxidation, and oxidative phosphorylation; with various fuel sources utilized to produce the intermediates necessary for each pathway. Alteration of immune cell metabolic programming that affects these pathways can result in alteration of immune function. These findings have led to the burgeoning field of immunometabolism that has only recently emerged as a major area of research in the context of HIV infection. Here we review the immunometabolic dysfunction associated with HIV infection and how this relates to drivers of immune activation and major age-related comorbidities.

Immunometabolism in PLWH

Gene expression and metabolites of carbohydrate metabolism, amino acid metabolism, oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA) cycle are associated with immune activation and disease progression in PLWH [11,12,13••], highlighting the important role of immunometabolism during HIV infection. In the last decade, an increasing number of studies have examined the immunometabolic dysfunction characteristic of HIV infection. These studies are discussed below and summarized in Table 1.

In Vitro Effects of HIV on Monocyte, Macrophage, and T cell Immunometabolism—The susceptibility of CD4+ T cells to HIV infection is primarily governed by the metabolic activity of the cell and, once infected, CD4+ T cell metabolism becomes altered. Glucose is an integral fuel source for HIV-infected CD4+ T cells and is utilized primarily for glycolysis despite the presence of oxygen that can be used for OXPHOS (i.e., aerobic glycolysis) [14•]. Compared to uninfected CD4+ T cells, HIV-infected CD4+ T cells display increased glucose transporter-1 (GLUT1) expression, increased glucose uptake, increased lactate production, and upregulation of the glycolysis enzymes lactate dehydrogenase A (LDHA) and hexokinase-1 [15,16•,17]. The increased reliance on aerobic glycolysis is required for reverse transcription, integration, and virion production [16•,17], identifying the metabolic program of the CD4+ T cell as essential for productive HIV infection. Along these lines, the metabolically active effector memory CD4+ T cell subset is associated with productive infection, whereas naïve and central memory CD4+ T cell subsets are associated with latent infection [16•].

In addition to increased aerobic glycolysis, HIV-infected CD4+ T cells repurpose their metabolic machinery using substrates of the TCA cycle [16•,18•]. The amino acid glutamine is used as a fuel source to repurpose the mitochondrial machinery and has been shown to be required for productive HIV infection [16•,18•]. Fatty acid oxidation was also identified as an energy source available to HIV-infected CD4+ T cells; however, glucose and glutamine are preferred [16•]. The concentrations of TCA cycle metabolites can also be affected by HIV factors. For example, treatment of Jurkat T cells with Tat alters mitochondrial machinery and increases production of succinate and malate in the TCA cycle [19]. A recent study in mice showed that increased CD4+ T_H1 cell succinate promotes IFN-γ production and that the mitochondrial malate-aspartate shuttle is essential for gene regulation and proliferation of CD4+ T_H1 cells [20].

Monocytes and macrophages can also be permissive to HIV infection. Similar to CD4+ T cells, the metabolic program of macrophages is affected by HIV infection [21•]. U937 monocyte-derived macrophages treated with the HIV viral protein Vpr increase their metabolic activity with increases in the following glycolytic enzymes: the hexokinase 1 (HK1), hexokinase 2 (HK2), glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase M2 (PKM2) [22]. However, examination of primary human monocyte-derived macrophages latently infected with HIV did not show alterations in glycolysis, rather, they displayed mitochondrial dysfunction as evidenced by enlarged mitochondria and decreased OXPHOS [21•]. These latently infected macrophages also utilize glutamine as a major energy source [21•]. The use of glutaminolysis has been shown to maintain ROS homeostasis that may promote the survival of HIV infected macrophages [23].

Ex Vivo and In Vivo Effects of HIV on Monocyte, Macrophage, and T cell Immunometabolism—Both T cell and monocyte/macrophage immunometabolism has been assessed in PLWH. Compared to CD4+ T cells from people without HIV, CD4+ T cells and monocytes from treated PLWH have increased markers of activation and increase their reliance on aerobic glycolysis as evidenced by increased expression of GLUT1 and increased lactate production [24,25]. Assessment of monocyte subsets in treated PLWH show that the highest increase in the rate of glycolysis is seen in intermediate monocytes (CD14+CD16+) which have been shown to be pro-inflammatory and are expanded in PLWH [4,25]. These data suggest that the increased aerobic glycolysis in monocytes and T cells may contribute to the low-level chronic inflammation experienced by PLWH on ART. The increased proportion of CD4+ T cells expressing GLUT1 is negatively correlated with total CD4+ T cell percent in treated PLWH but not in people without HIV, providing a potential link between immunometabolism and decline of CD4+ T cells [26,27]. A study examining metabolite levels in plasma from elite controllers that spontaneously lose virological control identified increased lactate levels, indicative of increased aerobic glycolysis during viral rebound and immune dysfunction [13••].

Mitochondria have also been implicated in the dysfunctional immunometabolism in PLWH. GLUT1 expression on CD4+ T cells is associated with increased mitochondrial density and membrane potential in treated PLWH [24], but there is a decreased oxygen consumption rate (OCR), indicating a repurposing of the mitochondria in CD4+ T cells from solely oxidative phosphorylation during chronic HIV infection [26,28••]. A possible explanation

is the utilization of alternate fuel sources in the TCA cycle as it was observed that the TCA cycle intermediate alpha-ketoglutarate increases along with a decrease in the amino acid fuel source glutamate in the plasma of elite controllers that lose virological control [13••]. Dysfunctional mitochondria can result in increased reactive oxygen species (ROS) production and oxidative stress. HIV-specific CD8+ T cells from PLWH have increased mitochondrial mass and ROS production compared to CD8+ T cells from people without HIV [29]. In CD4+ T cells and CD8+ T cells, oxidative stress is associated with IL-7 unresponsiveness, a lower CD4 count and increased production of cytokines [30].

Effects of HIV on Immunometabolism of Other Immune Cells—In addition to monocytes, macrophages and T cells; NK cells and B cells also play a pivotal role in controlling an HIV infection but there is a paucity of immunometabolism data for these cells in PLWH. When compared to T cells, peripheral NK cells and B cells from ART naïve PLWH are less bioenergetic, however, both are able to undergo metabolic reprogramming to achieve efficient function [28••,31,32]. A recent report shows that NK cells from untreated PLWH have decreased oxidative phosphorylation and glycolysis compared to people without HIV but there was no difference between treated PLWH and people without HIV [28••]. However, it has been shown that NK cells require prolonged stimulation in the presence of IL-15 to observe any metabolic differences with the method used [32]. Similar to NK cells, peripheral B cells showed no difference in either oxidative phosphorylation or glycolysis when comparing either treated or untreated PLWH with people without HIV, but B cell metabolic reprogramming has been shown to be influenced by the microenvironment and the immunogenic stimulant which can be very different *in vivo* [28••]. These data highlight the need for more studies to further classify the metabolic program of NK cells and B cells in PLWH.

Factors Contributing to Dysfunctional Immunometabolism in PLWH

Treatment of PLWH does not completely normalize immunometabolism to levels of healthy people without HIV [24,25]. This is likely due to a combination of different immune stimulating factors that may include microbial translocation of immunogenic products from the gut into circulation, chronic co-infection with cytomegalovirus (CMV), residual HIV production, gut microbial dysbiosis, and antiretroviral drugs. Each of these factors could potentially affect the metabolic state of immune cells but most have not been investigated as factors driving immunometabolic dysfunction in PLWH. These factors are described below and a model depicting their effect on the immunometabolism of CD4+ T cells is shown in Figure 1.

Microbial Translocation—During HIV infection the gastrointestinal mucosa undergoes irreversible damage [33–35]. The damaged mucosal barrier allows low levels of microbial components and microbes themselves to traverse the mucosa in a process referred to as microbial translocation (reviewed [36]). As microbes and some components of microbes are recognized by pattern recognition receptors (e.g., toll-like receptors) that stimulate immune cells, they could potentially serve as a chronic source of low-level immune stimulation. Both LPS and markers of immune activation are elevated in PLWH, and although reduced with antiretroviral therapy, both remain elevated compared to people without HIV [37]. Studies

in acutely SIV-infected pig-tailed macaques show that treatment with sevelamer, a drug that reduces systemic LPS levels, decreases immune activation [38]. In contrast to these studies, microbial translocation is similar between Ugandan children with and without HIV and is not associated with markers of immune activation, indicating that microbial translocation may not be a major cause of immune activation in all settings [39]. In addition, human studies that reduced systemic LPS levels pharmacologically with sevelamer or rifaximin had minimal to no effect on immune activation [7,40]. It remains to be determined whether microbial translocation is linked to immunometabolic perturbations in PLWH.

Microbial Metabolites—In addition to the structural damage that occurs in the gut mucosa, HIV infection also causes microbial dysbiosis in the gut [41–43]. The gut microbiome is less diverse in PLWH and is associated with increased monocyte activation [44]. This microbial dysbiosis is associated with decreased levels of bacteria that produce butyrate [45•], a short chain fatty acid (SCFA) that induces differentiation of regulatory T cells [46,47], and dampens monocyte, macrophage and dendritic cell inflammatory responses [47–49]. Many immune cells express SCFA receptors that, when stimulated, can impact cell function [50]. Administering prebiotics to PLWH can increase butyrate producing bacteria and dampen markers of immune activation [51]. Recently, incubation of human macrophages with butyrate was shown to decrease glycolytic metabolism [52].

Gut microbes can catabolize tryptophan into a number of metabolites that can interact with immune cells. Microbial dysbiosis in the gut of PLWH has been linked to increased microbial tryptophan metabolism and immune activation [41,53]. PLWH have evidence of increased tryptophan catabolism via the kynurenine pathway [54], with a resulting increase in the kynurenine to tryptophan ratio that is associated with atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (DM) [53,55•]. These tryptophan metabolites have been shown to be active on human T cells, causing decreased differentiation of Th17 cells and increased differentiation of Treg cells [54]. However, a recent study did not identify microbial tryptophan catabolizing enzymes (e.g., IDO-1) in the metatranscriptome of PLWH [56]. These differing results may be due to different study population characteristics. Host cells are also capable of metabolizing tryptophan via the kynurenine pathway, making it less clear if the increased kynurenine to tryptophan ratio observed in PLWH arises from tryptophan catabolism by microbial cells, host cells, or a combination of both.

Trimethylamine-N-oxide (TMAO) is a metabolite produced by select gut bacteria that metabolize choline and L-carnitine. Although most studies show no difference in TMAO levels in PLWH and people without HIV [57,58], TMAO levels in PLWH have been linked to atherosclerotic CVD and immune activation [59–61]. However, not all studies have demonstrated this linkage [57,62,63] and it remains unknown if and how TMAO can affect immune cells.

Cytomegalovirus—CMV infection is nearly universal in PLWH but does not usually cause any overt signs of disease in non-immunosuppressed PLWH [64,65]. A substantial proportion of CD4+ and CD8+ T cells are CMV-specific in PLWH, and although ART treatment alleviates CMV viremia, CMV-specific T cells either remain elevated or even increase [64,66]. In addition to the high level of CMV-specific T cells in treated

PLWH, markers of inflammation and immunosenescence are elevated compared to treated PLWH without CMV infection [67,68]. CD8+ T cell markers of immunosenescence are also increased in CMV-infected ART-treated PLWH compared to ART-untreated PLWH, however, they are at levels lower than CMV-infected, people without HIV, raising questions as to the role of CMV-associated immunosenescence in the context of HIV infection [69].

Detection of CMV DNA, but not EBV DNA, in ART-treated PLWH is associated with CD4+ T cell activation [70,71••], indicating that not all herpesviruses are associated with immune activation. Further supporting the role of CMV as a cause of immune activation, valganciclovir treatment of CMV-infected ART-treated PLWH with CD4+ T cell counts <350 cells/mm^3 results in a reduction of CD8+ T cell markers of activation [72]. In the same study, valganciclovir had little impact on DNA detection of EBV, HHV-6 and HHV-8, providing further evidence as to the specificity of CMV, and not other herpesviruses, driving T cell activation [72]. How CMV influences immunometabolism in the context of HIV infection has not been examined.

Viral Reservoir—Adherence to contemporary antiretroviral therapy can reduce HIV viral loads to undetectable levels by traditional quantitative assays. However, ultra-sensitive assays that can detect a single viral copy per milliliter show that low levels of virus are detectable for most PLWH [73]. Whether this residual low-level viremia represents production or replication of HIV is not universally agreed upon [74,75]. Regardless, low level viremia detected by ultrasensitive assays is associated with soluble immune activation markers [76], and in poor immunologic responders, associated with cellular immune activation markers [77]. Interestingly, one study showed that CMV- and EBV-specific CD4+ T cells are preferentially infected with latent HIV [78•], linking herpesvirus co-infection with immune activation and potentially virus production. A study that examined virologically suppressed treated PLWH showed a correlation between residual viremia, using an ultra-sensitive assay, and microbial translocation [79]. These studies demonstrate the interrelatedness of factors that may contribute to immune activation and dysfunctional immunometabolism in the context of HIV infection.

Antiretroviral Therapy—ART can have a direct effect on the mitochondrial function of immune cells [28••,80–82,83•]. Nucleoside reverse transcriptase inhibitors (NRTI) are a major cause of T cell mitochondrial dysfunction because they directly inhibit DNA polymerase-γ which is integral for mtDNA replication [84]. The NRTI tenofovir decreases mitochondrial respiration which may be caused by a decrease in expression levels of pyruvate dehydrogenase A (PDHA) and succinate dehydrogenase B (SDHB) [82]. Recent reports show that the effect of ART on mitochondria is not limited to the NRTI class, as integrase strand inhibitors (INSTI) and protease inhibitors (PI) reduce mitochondrial respiration in CD4+ T cells and increase ROS production [28••,85]. CD4+ T cells treated with NRTI, non-nucleoside reverse transcriptase inhibitors (NNRTI), INSTI and PI showed no differences in the expression of HIF1α, GLUT1 or PGK1, suggesting that ART effects on immunometabolism do not involve the glycolysis machinery [28••]. These studies highlight that ART may contribute to dysfunctional immunometabolism through altering mitochondrial function.

Implications of Dysfunctional Immunometabolism to Age-related Diseases

PLWH display an aged immune cell phenotype earlier than age-matched individuals without HIV [86]. In addition, as PLWH live longer due to ART, aging exacerbates chronic immune activation and exhaustion, microbial translocation and dysbiosis, CMV reactivation and immune response [87–91]. Immunometabolism is likely an important mediator of this aging process and associated age-related disease.

Cardiovascular Disease—In the ART era, CVD is a leading cause of morbidity and mortality in PLWH [92]. PLWH, both men and women, are at an increased risk of coronary artery disease and myocardial infarction (MI) [93,94]. Although coronary artery disease is the most frequent form of cardiovascular disease in PLWH, there is also increased risk for other types of cardiovascular diseases, including stroke [94], ventricular dysfunction and heart failure [95], myocardial steatosis and fibrosis [96,97], atrial fibrillation [98], and pulmonary arterial hypertension [99].

Inflammation plays an integral role in the development of atherosclerosis and subsequent cardiovascular events [100]. The association of increased inflammation and the increased risk of CVD has been identified in both individuals without HIV and PLWH, but may be heightened in PLWH [101,102•]. Increased inflammation in PLWH, as measured by plasma levels of sTNFR-I and sTNFR-II, is associated with increased incidence of MI and stroke [7]. Additionally, IL-6, sIL-2R and D-dimer are associated with increased carotid artery intima-media thickness (CIMT) in treated women with HIV [103]. Immune activation is mediated by monocytes/macrophages and T cells as activation of these cell types is associated with the presence of carotid artery lesions and coronary plaques in PLWH [104,105]. Monocytes from PLWH are activated and have elevated prothrombotic tissue factor expression, which exacerbates the development of the atherosclerotic plaque [106,107••]. It is unclear as to the HIV-specific drivers of increased CVD risk, but both LPS and CMV have been directly implicated. LPS was shown to drive immune activation of monocytes and subsequent coagulopathy in an SIV model, thereby linking the microbial translocation product LPS to immune activation and CVD [107••]; and the immune response to CMV is associated with atherosclerotic CVD for PLWH [108–110]. Additionally, TMAO concentration is associated with the number and severity of plaques in PLWH as well as immune activation and inflammation [59,61]. In a population of mostly ART-treated women with suppressed HIV infection, inflammatory monocyte GLUT1 expression was identified to be associated with cardiovascular disease markers and subclinical atherosclerotic cardiovascular disease [111••,112••], linking immune activation, immunometabolism and co-morbid cardiovascular disease.

Diabetes Mellitus—DM is more prevalent in PLWH compared to individuals without HIV, including a higher prevalence for younger non-obese PLWH [113••]. In the United States, DM prevalence for PLWH has increased from ≈ 0% in the pre-ART era to 6.8% −11.8% in the modern ART era, highlighting the increasing importance of DM in PLWH [6,113••,114]. Increasing prevalence of type 2 DM in PLWH has also been shown in African countries, with higher prevalence of type 2 DM in PLWH compared to persons without HIV,and an even higher prevalence for untreated PLWH [115]. The increased prevalence of

DM in PLWH occurs in the absence of traditional risk factors, indicating the presence of HIV-specific factors in DM development [113••].

DM is now considered an inflammatory disease [116], and in PLWH DM is associated with activation of T cells and monocytes [53,117]. ART-treated PLWH with DM have increased inflammation, expression of CD4+ T cell GLUT1, and increased CD4+ T cell metabolic activity compared to those without DM [118]. Additionally, CD8+ T cells and monocytes from PLWH with DM compared to those without DM have increased expression of GLUT1 (Butterfield TR, unpublished data). In a pathogenic SIV model, increased peripheral CD8+ T cells and increased inflammatory cytokine production was associated with a 2.6-fold decrease in GLUT4 (GLUT most responsive to insulin) expression on adipocytes [119•]. An analysis of insulin resistance in PLWH identified a negative correlation between HOMA-IR and expression of the monocyte electron transport chain (ETC) gene NDUFS7, inflammatory signaling pathway gene MAPK11, and adipokine signaling pathway gene CMKLR1 [120]. These findings provide evidence for immunometabolic perturbations in PLWH with DM and a potential linkage of systemic insulin resistance and the metabolic and activation state of monocytes.

Adipose tissue is an environment of adipocytes closely associated with macrophages and T cells, which communicate via cytokines to either maintain metabolic homeostasis or contribute to metabolic disorders [121,122]. Adipose tissue has been identified to play a key role in the development of insulin resistance, DM and other inflammatory conditions, as well as serving an additional role in PLWH as a possible reservoir for memory CD4+ T cells that harbor HIV [123]. The proportion of activated CD4+ T cells from adipose tissue of PLWH increases with increasing glucose intolerance [124•]. Most of these CD4+ T cells are of the effector memory phenotype which are more responsive to stimulation, suggesting that adipose tissue may provide a setting for chronic stimulation of CD4+ T cells in PLWH [124•]. These memory CD4+ T cells rely heavily on fatty acid oxidation (FAO) for proliferation and survival [10] and the byproducts of FAO, the acylcarnitines, are associated with DM and IR in PLWH [125,126]. Taken together, these findings suggest a role for the interaction between adipocytes and memory CD4+ T cells in the increased risk of DM in PLWH.

The availability and metabolism of amino acids in immune cells has also been shown to be associated with DM in PLWH. The plasma level of tryptophan is decreased, while the Kyr/Trp ratio is increased in PLWH with DM, indicating increased catabolism of tryptophan, though the cell type(s) responsible for the catabolism of tryptophan is unknown [53,127]. Tryptophan catabolism in PLWH with DM is associated with increased inflammation [53,125,127]. CMV-specific antibodies in PLWH have also been linked to inflammation and are associated with insulin resistance, supporting increased inflammation and immune activation with the development of DM in PLWH [128].

Cancer—Mortality from non-AIDS defining cancers (NADC) is increased in PLWH compared to people without HIV, with more severe forms at diagnosis [129,130]. During 2006–2009 in the United States, 10% of mortality in PLWH was attributable to NADC, which increased each year over the study period of 1995–2009 [131]. The incidence of

NADC increased from 31.4% in the pre-ART era of 1991 – 1995 to 58% in the early-ART era of 1996 – 2002 [132]. The risk factors for cancers in PLWH include traditional risk factors such as smoking for lung cancer and age for all cancers [131,133,134]. However, when calculated risk is adjusted based on traditional risk factors, PLWH continue to have a higher risk for cancer compared to people without HIV [133,134]. These studies highlight the burden of cancers in PLWH on ART and that there are HIV-specific risk factors for cancer.

Immunometabolic dysfunction and inflammation experienced in PLWH may create an environment that promotes tumor growth. Increased IL-6 plasma concentration is associated with increased risk of developing cancer in PLWH, implicating inflammation in oncogenesis in PLWH [135]. It is believed that pulmonary inflammation and repeated infections result in the increased risk for lung cancer and that the immune dysfunction experienced even on ART plays a role in increased NADC risk [136,137]. In people without HIV an increased Kyr/Trp ratio is also implicated in the immunosuppressive environment that promotes tumor growth but has not been investigated in the context of HIV infection [138]. Furthermore, studies in people without HIV have shown that increasing lactate concentrations suppress the anti-tumor response [139,140], a process that could be exacerbated in PLWH considering the increased aerobic glycolysis [24,25] and plasma concentrations of lactate [13••].

Other Diseases—The age-related diseases discussed above are some of the most common and researched for PLWH, but others such as frailty and HIV-associated neurocognitive disorders (HAND) have also been investigated in the context of immunometabolism. Frailty, a condition characterized by physical slowness, fatigue, low activity, weakness and physical shrinking in the elderly, occurs at a younger age in PLWH [4,141] and is associated with increased measures of inflammation in PLWH [142,143]. Monocyte glycolytic metabolism and activation may be important for the development of frailty in PLWH, as increased expression of GLUT1 on monocytes is associated with frailty in treated PLWH [143,144•]. HIV-associated neurocognitive disorder (HAND) is also a major co-morbid condition in PLWH as more than half of PLWH are affected HAND [145]. Inflammation and viral replication in viral reservoirs appear to be the most integral factors leading to the burden of HAND in PLWH [146,147]. Markers of inflammation, T cell activation, monocyte activation and viral replication are associated with the presence of HIV-associated dementia (HAD) in PLWH [146,147] and CMV antibody response is associated with decreased neurocognitive performance in PLWH [148]. These age-related conditions are important risk factors for each other as it has been shown that neurocognitive decline in PLWH is a risk factor for frailty [149] and CVD and DM are independent risk factors for HAND [150]. This is further underscored by the fact that a number of PLWH present with more than one co-morbid condition [151,152].

Conclusion

HIV immunometabolism studies have increased dramatically in recent times, yet many important questions remain. The relationship between HIV-specific immune stimuli and immunometabolism is unknown and only a very small number of studies have investigated immunometabolism in the context of age-related diseases. Drug targeting of

immunometabolism has become a major area of investigation that could have therapeutic potential in the context of age-related disease in PLWH but remains unexplored. Future investigation of these topics will be important to more completely understand the role of immunometabolism in PLWH.

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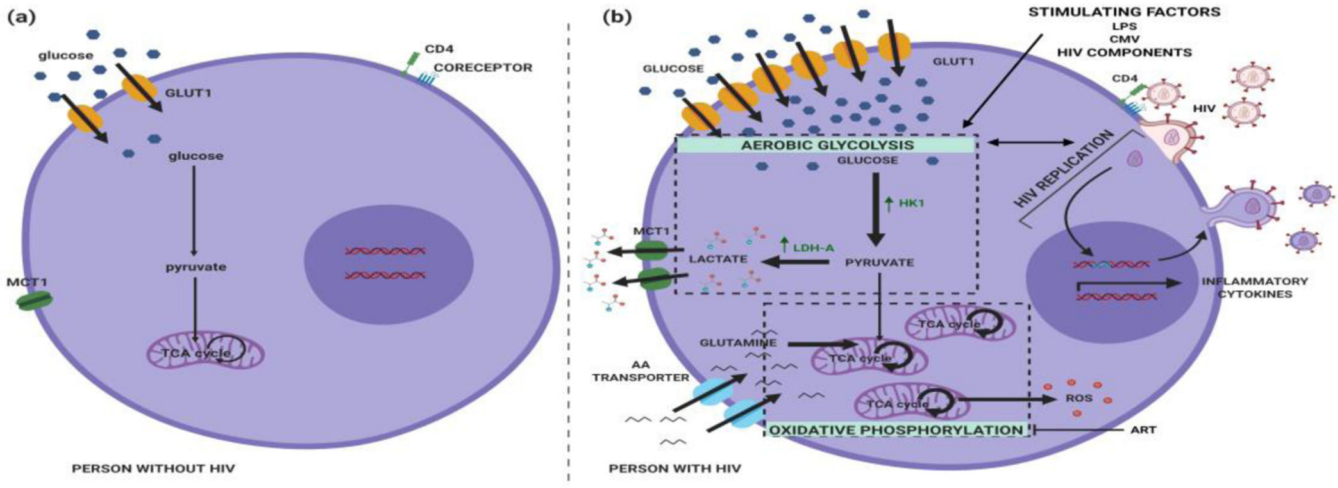

Figure 1. Model of CD4+ T cell immunometabolism during HIV infection.

(**a**) Representation of a resting CD4+ T cell from a person without HIV. In the absence of stimulating factors, glucose is metabolized into pyruvate and is then further metabolized by entering the TCA cycle. Aerobic glycolysis, lactate production, amino acid utilization and production of inflammatory cytokines are absent. (**b**) Representation of a CD4+ T cell from a PLWH. Aerobic glycolysis may be initiated after stimulation of CD4+ T cells with lipopolysaccharide, cytomegalovirus, HIV components (e.g. Tat and Vpr) and/or replication of HIV. Initiation of aerobic glycolysis is accompanied by increases in glucose consumption, glucose transporter-1 surface expression, hexokinase-1 expression, and lactate dehydrogenase-A expression. HIV infection also augments mitochondrial respiration as CD4+ T cells utilize alternative fuel sources such as glutamine for oxidative phosphorylation and antiretroviral therapy impairs the electron transport chain and increases reactive oxygen species production. These changes in glycolysis and oxidative phosphorylation in CD4+ T cells from PLWH are associated with increased expression of inflammatory cytokines and increased reactive oxygen species. (Abbreviations: AA transporter – amino acid transporter, ART – antiretroviral therapy, CMV – cytomegalovirus, GLUT1 – glucose transporter-1, HK1 – hexokinase-1, LDH-A – lactate dehydrogenase-A, LPS – lipopolysaccharide, MCT1 – monocarboxylate transporter 1/2, ROS – reactive oxygen species, TCA cycle – tricarboxylic acid cycle)

Table 1.

Summary of dysfunctional immunometabolism in HIV infection

Metabolic Modulation	Cell Type	Implications for PLWH	References
Increased glucose uptake and expression of GLUT1 and HK1	CD4+ T cells, CD14+CD16+ Monocytes, Macrophages	Productive infection and susceptibility to infection	Palmer, 2013; Palmer, 2014; Hegedus, 2014; Loisel Meyer, 2012; Barrero, 2013; Masson, 2017
		Activation	
		Secretion of inflammatory cytokines	
		Decline in CD4 count	
Increased lactate secretion and expression of LDHA	CD4+ T cells, CD14+CD16+ Monocytes	Activation	Liao, 2012; Palmer, 2013
		Secretion of inflammatory cytokines	
Increased intracellular glutamine	CD4+ T cells, Macrophages	Productive infection	Hegedus, 2017; Datta, 2016
		Survival of chronically infected cells	
Increased intracellular glutamic acid and α-ketoglutarate	Macrophages	Survival of chronically infected cells	Datta, 2016
Increased ROS production	CD4+ and CD8+ T cells, Macrophages	Survival of chronically infected cells	Castellano, 2019; Datta, 2016; Kalinowska, 2013; Masson, 2017
		Unresponsiveness to IL-7	
Increased fatty acid metabolism	Macrophages	Survival of chronically infected cells	Castellano, 2019; Datta, 2016
Increased mitochondrial density and hyperpolarized mitochondria	CD4+ and CD8+ T cells	Increased sensitivity to apoptosis	Kalinowska, 2013; Masson, 2017
		Unresponsiveness to IL-7	

Abbreviations: GLUT1 – Glucose transporter-1; HK1 – hexokinase-1; LDHA – Lactate dehydrogenase A; ROS – reactive oxygen species.