Current topics in HIV-1 pathogenesis: The emergence of deregulated immuno-metabolism in HIV-infected subjects

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Abstract. HIV-1 infection results in long-lasting activation of the immune system including elevated production of pro-inflammatory cytokine/chemokines, and bacterial product release from gut into blood and tissue compartments, which are not fully restored by antiretroviral therapies. HIV-1 has also developed numerous strategies via viral regulatory proteins to hijack cell molecular mechanisms to enhance its own replication and dissemination. Here, we reviewed the relationship between viral proteins, immune activation/inflammation, and deregulated metabolism occurring in HIV-1-infected patients that ultimately dampens the protective innate and adaptive arms of immunity. Defining precisely the molecular mechanisms related to deregulated immuno-metabolism during HIV-1 infection could ultimately help in the development of novel clinical approaches to restore proper immune functions in these patients.

1. Introduction: when metabolism meets immunology.

Immunology and metabolism have always been considered as distinct disciplines. However, recent advances in the understanding of immune functions under normal and disease conditions associate these branches with intricate networks. In this context, most cancer cells predominantly undergo high rate of glycolysis, up to 200 times higher than those of their normal tissues even in the absence of oxygen. Such effect is called "Warburg effect" and results in major changes in inflammation and the immune response [1-3]. Thus immuno-metabolism has become a burgeoning field of research, dissecting the crosstalk between key metabolic pathways and immune cell development, fate, and behavior in the context of physiologic processes, anti-tumoral and anti-microbial defense. The immuno-metabolism underlies each aspect of our lives representing all nutriment

transformations that are required for every function and physiological process spanning from hematopoietic cell development to microbial defense. Mounting an immune response *per se* requires major changes to metabolic processes, since significant amounts of energy and molecule biosynthesis are needed for both innate (pro-inflammatory cytokine/chemokine release, antigen processing, and phagocytose from monocyte/macrophages and dendritic cells; DC) and adaptive arms of immunity (T-cell differentiation, proliferation and IFN-γ production) [4-6]. The fact that the metabolism is intimately involved in immune cell regulation and physiology is of particular relevance in the context of HIV-1 infection, since the virus is entirely dependent on the host cells for providing the metabolic resources for completion of the viral replication cycle and the production of virions [7].

2. Immuno-metabolism in HIV-1-infected patients: from friend to foe.

In addition to the progressive loss of CD4 T-cells, HIV-1 infection is characterized by hyper immune-activation, persistent inflammation, and elevated pro-inflammatory cytokine/chemokine (IL-1β, IL-6, IL-18, TNF-α, and interferon γ-inducing protein 10; IP-10) released from monocyte/macrophages everywhere in the organism [8, 9]. A hallmark of acute phase of HIV-1 primary infection is the disruption of gut integrity and subsequent release of bacterial products within the bloodstream and lymphoid tissues, increasing the immune activation/inflammation [10, 11]. It is worth noting that, even if antiretroviral therapy (ART) is effective in suppressing viral replication and significantly increasing life-expectancy of treated patients, it does not fully inhibit HIV-1-related inflammation, particularly in the gut [12-15]. Since metabolism control depends on

signals that are deregulated during HIV-1 infection, it is not surprising that infected patients, even those under ART, display a number of systemic metabolic abnormalities that negatively impact the immune functions and contribute to viral pathogenesis (Fig.1).

3. Oxidative stress during HIV-1 infection

3.1. *Physiologic functions of reactive oxygen species (ROS)*. ROS are chemically highly reactive molecules containing oxygen, such as hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\cdot}$-), nitrite oxide ($NO^{\cdot}$), and hydroxyl radical ($OH^{\cdot}$). These molecules are formed as natural by-products of the physiological metabolites of oxygen, playing a key role in cell signaling, homeostasis, and are also required to ensure anti-tumoral and anti-microbial protection [16-18]. Over-production of ROS occurring upon inflammation-related diseases results in the establishment of oxidative stress, a deleterious process that can be an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA [19, 20]. Of note, ROS worsens inflammation status by promoting the production of pro-inflammatory cytokines including IL-1β, IL-6, interferons (IFN) and TNF-α that subsequently induces further ROS generation. To protect itself against oxidative stress, the immune system has at its disposal a number of (*i*) antioxidant enzymes including superoxide dismutase (SOD), catalase, glutathione peroxidase/reductase, (*ii*) vitamins, such as vitamin A, C and E, and (*iii*) small redox proteins such as glutathione (GSH) and thioredoxin (THX).

3.2. *Elevated levels of ROS during HIV-1 infection*. HIV-1 infection has been associated with profound deregulation of ROS production and the antioxidant system. For instance, HIV-1-infected patients exhibit increased oxygen consumption rates, elevated plasmatic

levels of hydroperoxides, oxidized low density lipoprotein (oxLDL), and malondialdehyde (MDA), both by-products of lipid peroxidation [21, 22], whereas their GSH, SOD and THX levels are significantly reduced [23, 24]. There is now convincing evidences that both HIV-1-related inflammation and viral proteins such as Tat, Vpr, Nef, and Gp120 can induce ROS production, which further results in significant immune dysfunction and several tissue injuries (Table 1).

3.3. *Impact of HIV-1-related oxidative stress on T-cell function and survival*. HIV-1 can hijack host cellular machinery to its benefit by producing higher amounts of ROS in T-cells. ROS induce HIV-1 long terminal repeat (LTR) and viral replication via post-translational regulation of Nf-κB [25]. In this context, HIV-1 regulatory protein Tat has pro-oxidant properties via the activation of NADPH oxidase and the inhibition of intracellular GSH levels, which contributes in inducing LTR transactivation [26-28]. The viral protein Vpr also activates the oxidative stress pathway to positively regulate HIV-1 promoter, but in a hypoxia factor 1 alpha (HIF-1α)- and MAP_3K_7-dependent manner [29, 30]. Of note, the elevated ROS production occurring in T-cells during HIV-1 infection results in reduced response to γ-chain receptor cytokines, T-cell dysfunction, and cell death. Several studies demonstrated that HIV-1-induced T-cell apoptosis is mediated through oxidative stress in part by down-regulating vitamin D receptor (VDR) and inducing PD-1 expressions [31-33]. Furthermore, elevated ROS levels impair IL-7 responsiveness in CD8 and central memory CD4 T-cells from chronically-infected viremic patients [21]. Our own observations demonstrate that ROS negatively impact IL-2 signaling in memory CD4 T-cells during the early phase of primary infection, a defect that can be restored by the use of antioxidant N-acetyl cysteine (NAC) (J.vG. data not

published). Neutrophils purified from the blood of HIV-1-infected patients suppress T cell function (IFN-γ production) via several mechanisms including PD-L1/PD-1 interaction and production of ROS [34]. In turn, elevated TGF-β activation by ROS leads to the differentiation of HIV-1-infected CD4 T-cells into $FoxP3^{+}CD25^{+}$ immuno-suppressive T-regulatory (T_{reg}) cells [35].

3.4. *Adverse effect of HIV-1-related oxidative stress on myeloid cells*. Monocytes from HIV-infected patients spontaneously produced increased amounts of H_2O_2 that enhance cell activation and production of pro-inflammatory cytokines [36, 37]. The viral protein Nef also induces the release of superoxide anions from macrophages [38]. Enhanced ROS generation within macrophages during the course of HIV-1 infection results in cell depletion by TRAIL-induced apoptosis [39]. Activation of monocytes with IFN-α in HIV-1 infection increase ROS production and lipid peroxidation that may enhance cell activation [22, 37]. In the brain, activation of pro-inflammatory resident monocyte/macrophages contributes to the pathophysiology of severe cognitive problems, such as HIV-related dementia (HAD) and HIV-associated neurocognitive disorders (HAND) [40]. In this context, HIV-1-related oxidative stress mediates up-regulation of monocyte adhesion, and loss of neurons and astrocytes, and gene delivery of antioxidant enzymes (SOD, glutathione peroxidase) or NAC amide treatment restore effective neuroprotection [41-45]. Finally, HIV-1 Gp120 induces the expansion of immuno-suppressive $CD33^{+}CD14^{+}$ myeloid derived suppressor cells, which have the capacity to reduce IFN-γ release by activated T-cells, a phenomenon that is restored upon ROS inhibition [46].

4. Up-regulated tryptophan metabolism in HIV-1 infection.

4.1. *Physiologic function of L-tryptophan (Tryp) metabolism*. Tryp, one of eight essential amino acids found in the human diet, is tightly involved in a number of metabolic functions and has been widely used as an effective tools in clinical interventions [47]. Tryp catabolism generates by-products such as kynurenines (Kyn), precursors of several molecules including the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) that are key factors for redox reactions in all living cells. In hematopoietic cells, formation of Kyn is driven by the indoleamine 2,3-dioxygenase type 1 (IDO-1) that plays a key role in regulating T-cell-mediated immunity [48]. Several soluble factors including IFN-γ, TNF-α, IL-1β, soluble CD40 (sCD40), Toll-like receptor (TLR) ligation, CTLA-4, and IL-32, are known to induce IDO-1 activity that is characterized by a higher ratio of Kyn to Tryp (Kyn/Tryp ratio) [49-53] (Fig. 2). Strain-dependent HIV-1 infection, direct attachment of Gp120 to CD4, or Tat also induced IDO-1 activity through direct mechanisms, but also indirectly following IFN-γ production [54-58]. Since these molecules are usually up-regulated in HIV-1-infected patients, particularly those with detectable viremia and heightened inflammation [59], up-regulated IDO-1 activity in their system is expected.

4.2. *Elevated Tryp metabolism in HIV-1-infected patients*. A number of studies and reviews reveal that plasma from HIV-1-infected patients display reduced levels of Tryp, and up-regulated Kyn concentrations, indicating that HIV-1 infection is associated with tryptophan catabolism at higher rate [54, 60-65]. Elevated IDO-1 activity in HIV-1-infected patients positively correlates with inflammation markers such as neopterin, and negatively with CD4 T-cell counts [66, 67]. Whereas many studies demonstrate that ART

significantly reduced, but fails to normalize IDO-1 activity to levels observed within the control uninfected subjects [65, 67, 68], recent data provided by Jenabian M-A. *et al.* show full normalization of IDO-1 activity in ART recipients with their cohorts of subjects [11]. This discrepancy is likely to be due the fact that last study included infected subjects who initiated ART within the first weeks of the primary infection, thus underscoring the benefit of early treatments to restore proper tryptophan metabolism. The Kyn pathway independently predicts poor CD4 T-cell count recovery and increased mortality among HIV-1-infected patients initiating ART [69, 70].

4.3. *Immuno-suppressive effects of elevated Kyn metabolism on adaptive and innate immune responses*. A. *Adaptive immunity*. Loss of Th_{22} cells, specialized in maintaining intestinal barrier integrity and in stimulating antimicrobial defence, is associated with increased immune activation and IDO-1 activity in HIV-1 infection, which can be partially reversed by ART [71]. By lowering the availability of Tryp, HIV-1 also inhibits CD4 T-cell proliferation by inducing IDO-1 in myeloid and plasmacytoid dendritic cells (pDC), an effect that is partially prevented by the use of IDO-1 competitive blocker 1-methyl tryptophan (1MT) [54, 57, 72, 73]. Furthermore IDO-1 signaling pathway is essential for pDC-mediated T_{reg} generation from CD4 T-cells and implicates the generation of Kyn and other Tryp catabolites as the critical factors of this process [74]. The increased Tryp catabolism observed in HIV-1-infected humans and SIV-infected macaques also correlates with the loss of Th_{17} cells, important players in mucosal immunity, thus changing the balance of Th_{17} to T_{reg} and increasing immuno-suppressive responses [61, 63, 75-77]. Interestingly, a small group of HIV-1-infected subjects, called elite controllers (EC) who are able to spontaneously control viral replication and to

display normal CD4 counts in the absence of ART [78], show similar IDO-1 activity compared to uninfected subjects [63]. This confirms the key role of Tryp metabolism in HIV-1 control and the maintenance of proper T-cell response [63]. Furthermore, increased IDO-1 activity in primary HIV-1-infected patients correlates positively with the levels of CD8 T-cell activation [11].

B. *Innate immunity*. In diverse anatomical compartments such as gut, lymph nodes and blood, the early induction of IDO-1 activity in macrophages, and dendritic cells dampens the antiviral responses and thus contributes to disease progression in SIV and HIV infections [52, 77, 79]. Elevated IDO-1 activity during primary infection positively correlates with monocytic pro-inflammatory cytokines including IL-6, IL-18, and TNF-α, and negatively with the frequency of dendritic cells [11]. Furthermore, increasing observations indicate that HIV-1 and SIV-1 infections mediate heightened production of toxic metabolites such as Kyn and quinolinic acids by brain-resident macrophages, contributing to the neuron/astrocyte cell death, and the neuropathogenesis of HIV-associated dementia (HAD) and HIV-associated myelopathy (HAM) [80-82].

5. Increased glucose metabolic activity during HIV-1 infection

5.1. *Glucose management, a key factor for bioenergetic needs, is deregulated in HIV-1 infection*. Glucose is readily utilized by cells of the immune system and is used to generate energy and biosynthetic precursors. Activation of immune cells is associated with increased glucose utilization and this is facilitated, in part, by increased expression of glucose transporters [83]. For instance, T-cell activation requires the up-regulation of glycolysis (catabolism of glucose) to meet the biosynthetic and bioenergic needs of cell

proliferation, survival, and immune function including the synthesis of cytokines [2, 5, 84]. As mentioned earlier, since HIV-1 infection is characterized by long-lasting and excessive inflammation/cell activation, most of infected patients display up-regulation in glucose metabolic activity [6, 85-88]. These observations are consistent with higher glucose uptake/trafficking in HIV-1-infected patients and elevated metabolite pool sizes such as sedoheptulose 7-phosphate and ribose-phosphate [86].

5.2. *High glucose up-take in CD4 T-cells enhances cell permissiveness to HIV-1*. HIV-1 infection causes an increase in glycolytic flux which brings the glycolytic capacity of primary infected CD4 T-cells close to its maximum [89]. The study shows that glycolysis is particularly required for virion production and additionally worsens the sensitivity of the infected cell to virus-induced apoptosis. Palmer C.S. *et al.* recently reported significant increase in the percentage of circulating CD4 T-cells expressing Glut-1 (major glucose transporter on T-cells) which is associated with cell activation and depletion during chronic HIV-1 infection and is not fully diminished following combination antiretroviral therapies [88]. Interestingly, IL-7 stimulation renders CD4 T-cells susceptible to HIV-1 entry by up-regulating the surface expression of Glut-1 and glucose transport into T-cells [90]. Hyperglycemia (condition with excessive amounts of glucose in plasma) also has the potential to enhance HIV-1 entry into T-cells through the up-regulation of CXCR4 expression [91]. Taylor H.E. *et al.* have shown that phospholipase D1 links T-cell activation signals to increased permissiveness to HIV-1 by triggering specific transcriptional programs involving glucose uptake and nucleotide synthesis [92].

5.3. *Protection of infected macrophages by counteracting glucose metabolism*. In contrast to infected CD4 T-cells, HIV-1-producing macrophages has significant reductions in

glucose uptake and steady glycolytic intermediates [86]. The viral protein Vpr, protects infected macrophages from apoptosis by the inhibition of hexokinase-1 (HK-1) activity, an enzyme that converts glucose to glucose-6-phosphate, therefore playing a non-metabolic role in maintaining mitochondrial integrity [93, 94]. HIV-1 Vpr can also hijack several pathways related to glucose management by inducing the expression of HK-1, glucose-6-phosphate dehydrogenase, and pyruvate kinase muscle type 2 [95].

6. Deregulation of lipid metabolism and compositions

6.1. *Physiologic function*. Lipids are fats that are either absorbed from food or synthesized by the liver. Triglycerides (TG) and cholesterol contribute most to diseases, although all lipids are physiologically important. Whereas, the primary function of TG is to store energy in adipocytes and muscle cells, cholesterol is a ubiquitous constituent of cell membranes, steroids, bile acids, and signaling molecules. All lipids are hydrophobic and mostly insoluble in blood, so they require transport within hydrophilic, spherical structures called lipoproteins. Lipoproteins are classified by size and density (defined as the ratio of lipid to protein) and are important because high levels of low-density lipoproteins (LDL), most cholesterol-rich of all molecules, represents a major risk factors for atherosclerotic heart disease.

6.2. *Lipid metabolism and composition during HIV-1 infection*. Following several years of HIV-1 infection, patients can develop multiple lipid abnormalities including insulin resistance, diabetes, hyperlipidemia and hypertension [96-99]. HIV-1 replication alone through the expression of viral proteins and the induction of inflammation can enhance

production of free fatty acids, LDL and many key enzymes and proteins involved in lipid metabolism such as fatty acid synthase and Apolipoprotein A-1 [100].

Furthermore, HIV-1 envelope-mediated membrane fusion occurs in cholesterol-rich lipid domains. In this context, the viral protein Nef can modulate the lipid composition of virion and host cell micro-domains ("lipid raft") to enhance virus infectivity and propagation, by specific enrichment of sphingomyelin and cholesterol specifically in these sites [101-103].

6.3. *Elevated lipogenesis, innate cells, and atherosclerosis incidence*. In addition to ROS production, the activation of monocytes with IFN-α during HIV-1-infection increases acetylated LDL up-take and synthesis, participating to the establishment of atherosclerosis and other arterial diseases [37, 104]. In fact, increased incidence to atherosclerosis and dyslipidemia (abnormal amount of lipids such as cholesterol in the blood) occurring in HIV-1-infected patients is tightly associated with up-regulated levels of pro-inflammatory cytokines such as IL-6 and TNF-α from activated monocytes/macrophages [105-107].

7. Foxo3a: potential candidate to explain deregulated immuno-metabolism in HIV-1.

Forkhead box O 3a (Foxo3a) is a transcriptional factor constitutively expressed on hematopoietic cells. In addition to pro-apoptotic and anti-proliferative targets, active Foxo3a induces the transactivation of genes implicated in the ROS detoxification (SOD, catalase) [79, 108, 109], and genes regulating glucose metabolism (glucose-6-phosphatase) [110, 111]. Although we and others have shown that HIV-1-infected

individuals display up-regulation in Foxo3a activity in infected macrophages, memory CD4 T-, and B-cells, even under ART, this leads to the expression of pro-apoptotic targets such as Bim, FasL, and TRAIL rather than metabolism-related genes [112-114]. However, the viral protein Vpr inhibits the ability of hypoglycemic peptide hormone insulin to suppress the transcriptional expression of glucose-6-phosphatase and SOD by inhibiting forkhead transcriptional factor (Foxo) activity in hepatocytes [115, 116]. Neurons undergo massive Foxo3a-dependent apoptosis in the presence of TNF-α and high glucose concentrations, conditions usually observed in infected patients developing HAD and HAND [117].

8. Modulation of autophagy in HIV-1 infection.

8.1. *Physiologic functions and impact on T-cells during HIV-1 infection*. Autophagy represents the basic catabolic mechanism that involves degradation of unnecessary or dysfunctional cellular components through the actions of specialized lysosomal structures called autophagosomes. The role of autophagy consists of degrading damaged or aged organelles, protein aggregates, but is also involved in microbial defence, antigen processing, and lymphocyte development and function [118-120]. Activation of autophagy occurs in response to nutrient deprivation, and recognition of pathogen associated patterns including HIV-1-related molecules [121-124]. In contrast to productively infected T lymphocytes, HIV-1-infected cells can induce autophagy in bystander uninfected CD4 T-cells through HIV-1 Gp120 exposure, leading to caspase-dependent apoptosis and cell depletion [126-129]. Interestingly, blood cells from HIV-1-infected elite controller subjects display more efficient autophagic response that leads to a

reduced viral production, thus confirming key role of autophagy in long-term immune protection against accelerated HIV-1-mediated disease progression [125].

8.2. *Autophagy in myeloid cell lineage in HIV-1*. Although there are relatively few studies that have assessed the role of autophagy in DC, Blanchet F.P. *et al.* show that exposure of DC to HIV-1 Gp120 down-regulates the formation of autophagic vacuoles, therefore resulting in altered cell response to LPS and increased DC-mediated HIV-1 trans-infection into CD4 T-cells [130]. During HIV-1 infection, IL-10, and viral proteins such as Tat and Nef suppress the induction of autophagy-associated genes (Beclin-1, autophagocytosis-associated protein 3; Atg-3) and inhibits the formation of autophagosomes in macrophages, dampening the anti-HIV-1 mechanism in these cells [131-133].

9. Potential strategies to restore proper immuno-metabolism in infected patients.

It now is well recognized by the scientific community that a large proportion of HIV-1-infected individuals, including those receiving ART treatment, can experience profound deregulations in immune-metabolism. Some of these metabolic defects may take place as early as the first weeks of primary infection, and might be reversed if ART is initiated during this early phase of infection [11]. However, ART usually improves, but does not always normalize all metabolic and clinical parameters (e.g. glucose uptake and gut inflammation) [12, 15, 88, 134]. Moreover, the long-term administration of antiretroviral molecules *per se*, particularly anti-proteases, results in abnormal fat distribution and impaired glucose homeostasis in more than 50% of treated patients [135-138]. Therefore

it is critically needed to develop new strategies aiming to improve metabolic conditions in HIV-1-infected patients in order to enhance innate and adaptive protective immunity.

The wise old saying, *we are what we eat*, may be particularly true in the context of immune fight against HIV-1. Although there is no clear evidence of beneficial effects of diets on premature immune ageing during chronic HIV-1-infection, the use of antioxidant vitamins, minerals, amino acids, and other dietary supplements is widespread in the HIV-infected community. Furthermore, enhancing the lifestyle represents another first-line approach, with a focus on smoking cessation in addition to exercise and diet modification (Mediterranean-style dietary pattern) to decrease cholesterol and triglyceride levels in HIV-1-infected patients [139-142]. Metformin and thiazolidinediones, molecules used to treat type 2 diabetes, have been shown to significantly improve glucose management, and prevent atherosclerosis in HIV-1 patients [143-145]. The *in vivo* administration of antioxidant N-acetylcystein amide or gene delivery of antioxidant enzymes is effective in protecting the blood brain barrier from oxidative stress-and inflammation-induced damage in Gp120- or Tat-exposed animals, and thus could be a viable therapeutic option for patients with HAD [41, 42, 146]. Similarly, the treatment of mice with 1-MT significantly inhibits IDO-1 activity, and enhance the elimination of virus-infected macrophages in an *in vivo* model of HAD [82]. In SIV-1-infected rhesus macaques, 1-MT synergizes with ART in inhibiting viral replication without interference with the beneficial immunologic effects of the antiretroviral treatment [147]. The administration of Niacin, a B vitamin, has shown encouraging preliminary results in reducing cholesterol and LDL, and reducing the levels of the up-stream Kyn in HIV-1-infected patients [148, 149]. A randomized trial is currently in progress to fully evaluate the potential benefit of

oral extended-release niacin in reducing immune activation, increasing CD4 T-cell recovery, and improving neurocognitive function in ART recipients [150].

10. Conclusion.

Despite the significant advances in HIV treatments and the reduction of both mortality and morbidity associated with infection, it is largely believed that current regimens cannot achieve HIV cure. This necessitates the implementation of complementary approaches by switching towards unconventional concepts. In this regard, there is now a growing evidence that deregulated immuno-metabolism represents a central element to the biased immunity against HIV-1 infection that leads to viral dissemination and pathogenesis. Understanding these immuno-metabolic defects in a timely manner and identifying novel biomarkers that can either predict or reflect their outcome is then a critical need in the fight against HIV and its associated clinical complications. This will ultimately pave the way to find innovative approaches to counteract these defects and reduce cell activation and chronic inflammation that will likely prevent massive T-cell loss and reinforce anti-HIV-1 defence and eventually achieve HIV cure.

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Figure legends.

Table 1. Host and viral molecules mediating oxydative stress in HIV-1-infected cells. This table also includes related health complications that occurs when the virus infiltrates tissues and induces heightened activation of resident macrophages.

Figure 1. Interplay between inflammation, viral proteins, prolonged HAART treatment, and deregulated metabolism resulting in immune dysfuntion and tissue injuries, particulalry at mucosal sites. In turn, gut mucosal insult leads to bacterial translocation that further fuels chronic inflammation and mediates metabolic defects. Other factors such as co-infections, drug abuse, and aging that could potentially interfere with and negatively impact on immuno-metabolism in infected subjects are also highlighted.

Figure 2. Schematic representation for the HIV-mediated deregulated tryptophan metabolism and the subsequent immune/tissue impairments during infection. (*i*) Increased IDO-1 activity leads to higher levels of tryptophan catabolites. Both kynurinine and the downstream quinolic acid mediates the initiation of HAD and HAND and (*ii*) Higher levels of tryptophan metabolism mediated by interaction of CTLA-4 (expressed by T-cells) with its ligands (B7-1 and B7-2) expressed by antigen presenting cells is also associated with profound effects in T-cell activation, cytokine production, proliferation and differentiation.

Table 1

Table 1

Cell type	Inducer	Oxidative stress	Host mechanisms	Immune Dysfunction	Reversibility	Reference
Adaptive Immunity						
$CD25^{neg}CD4$ T-cells	T-cell receptor triggering	↑($O2^{\cdot}$-)	↑(TGF-β; FoxP3)	↑Treg differentiation	yes	[35]
Jurkat cells	H_2O_2	/	↑(TNF-α; Nf-κB; TAK1; AP-1)	↑HIV-1 LTR activation	yes	[25]; [30]
$CD4^{+}$MAGI cells	Tat	↑(H_2O_2); ↓(GSH)	↑(Nrf2; Nox2; AKT; Nf-κB)	↑HIV-1 LTR activation	yes	[27]; [28]
CD8; memory CD4 T-cells	HIV-1 infection	↑(H_2O_2, MDA)	↓(induced pSTAT-5; CD127)	↓response to IL-7	non specified	[21]
T-cells	HIV-1 infection	↑(H_2O_2, $O2^{\cdot}$-)	↑(Ras; VDR methylation; PD-1)	↑T-cell apoptosis	yes	[31]; [32]; [33]
Innate Immunity						
macrophages	HIV-1 infection	↑(H_2O_2, O2.-)	↑(pJNK); ↓(TRAIL decoy receptors)	↑macrophage apoptosis	non specified	[39]
monocytes	HIV-1 infection; IFN-α	↑(ROS, oxLDL)	↑(LDL up-take; MX-1 and CXCL10)	↑inflammatory $CD16^{+}$monocytes	non specified	[22]; [37]
$CD33^{+}$MDSC	gp120; IL-6	↑(ROS)	↑(IL-6; pSTAT3)	↑MDSC; ↓ T-cell function (ROS dependent)	yes	[46]

Figure 1

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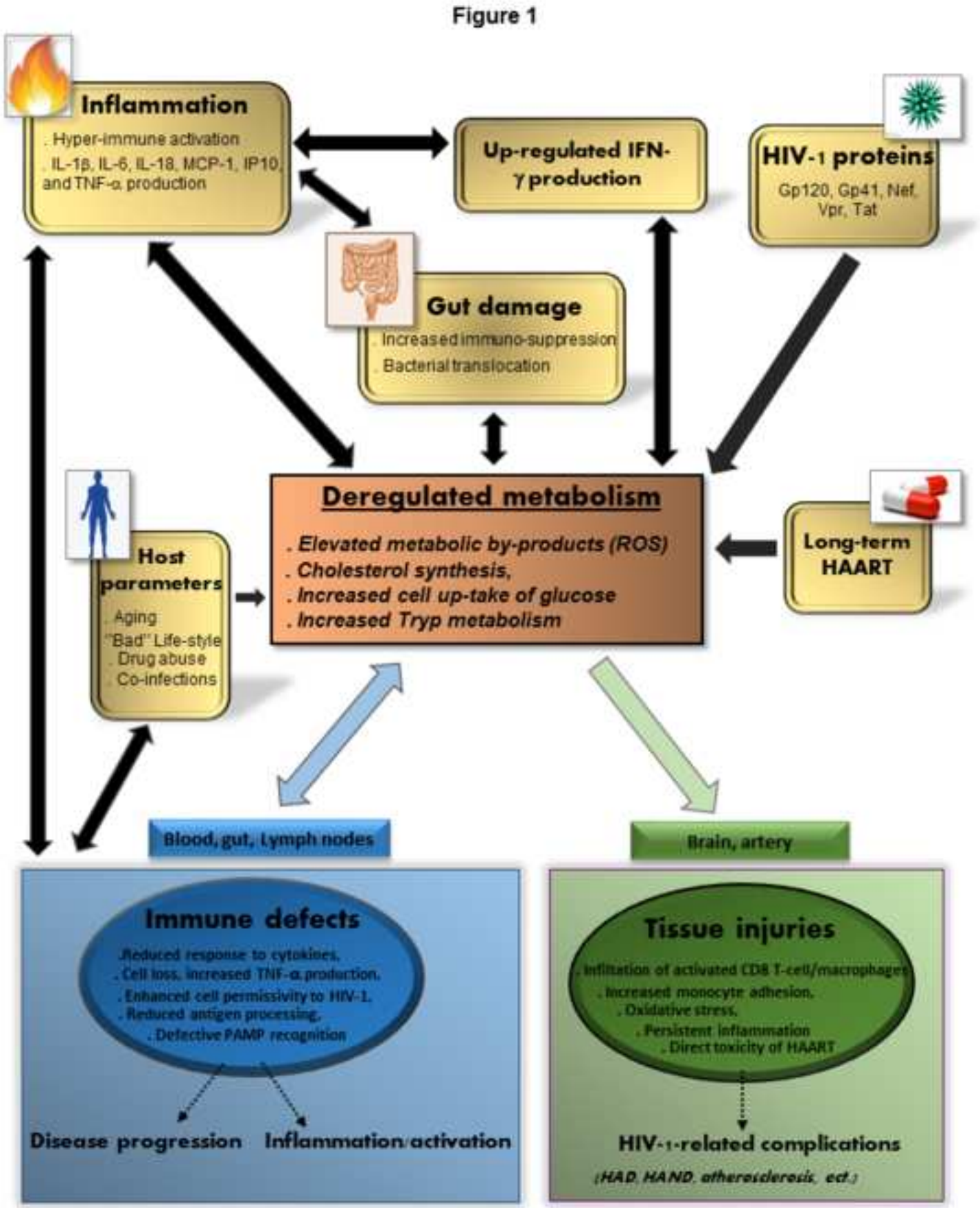

Figure 2

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Figure 2