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AIDS Rev. 2015;17:96-106

Clinical Relevance of Kynurenine Pathway in HIV/AIDS: An Immune Checkpoint at the Crossroads of Metabolism and Inflammation

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Abstract

Tryptophan degradation along the kynurenine pathway is associated with a wide variety of pathophysiological processes, of which tumor tolerance and immune dysfunction in several chronic viral infections including HIV are well known. The kynurenine pathway is at the crossroads of metabolism and immunity and plays an important role in inflammation while also playing an opposing role in the control of acute and chronic infections. In this review we have summarized findings from recent studies reporting modulation of tryptophan degrading the kynurenine pathway in the context of HIV infection. This immuno-metabolic pathway is modulated by three distinct inducible enzymes: indoleamine 2,3-dioxygenase 1 and 2 and tryptophan 2,3-dioxygenase. Increased expression of these enzymes by antigen-presenting cells leads to local or systemic tryptophan depletion, resulting in a mechanism of defense against certain microorganisms. Conversely, it can also lead to immunosuppression by antigen-specific T-cell exhaustion and recruitment of T regulatory cells. Recently, among these enzymes, indoleamine 2,3-dioxygenase 1 has been recognized to be an immune response checkpoint that plays an important role in HIV immune dysfunction, even in the context of antiretroviral therapy. In addition to the activation of the kynurenine pathway by HIV proteins Tat and Nef, the tryptophan-degrading bacteria present in the intestinal flora have been associated with dysfunction of gut mucosal CD4 Th17/Th22 cells, leading to microbial translocation and creating a systemic kynurenine pathway activation cycle. This self-sustaining feedback loop has deleterious effects on disease progression and on neurocognitive impairment in HIV-infected patients. Therapy designed to break the vicious cycle of induced tryptophan degradation is warranted to revert immune exhaustion in HIV-infected persons. **(AIDS Rev. 2015;17:96-106)**

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Key words

IDO. Kyn. Trp. HIV. Microbiota. Treg. Th17.

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Introduction

The hallmark of HIV infection is the progressive loss of CD4 T-cells in the context of chronic immune activation[1]. The persistence of immune activation even after several years of antiretroviral therapy (ART) is associated with an increased risk of AIDS and non-AIDS defining illnesses including cardiovascular, liver, and kidney diseases, cancers, and alteration of neurocognition[2]. In regards to the cause of chronic immune activation, HIV and associated coinfections like hepatitis C virus or cytomegalovirus (CMV) do not appear to be the sole contributors[3,4]. By hijacking the immune system, HIV is capable of drastically altering the gastrointestinal environment, leading to significant changes to the gut microbiota and mucosal permeability, resulting in microbial translocation from the gut into the peripheral blood[4]. Such changes made locally in the gut have far-reaching consequences as they contribute to create a state of systemic immune activation[5].

The markers to assess HIV immune activation linked to clinical outcome comprise the following: (i) elevated expression of activation markers HLA-DR/CD38 on T-cells, and (ii) heightened plasma levels of inflammatory cytokines/chemokines, type 1 interferons (IFN) and increased frequency of activated macrophages, dendritic cells (DC), and monocytes expressing $CD14^+CD16^+$ [6-9]. We and others have identified several factors associated with profound T-cell dysfunction linked to markers of immune activation[10-13]. Among these factors, the enhanced expression of inhibitory molecules like programmed cell death-1 pathway (PD-1/PDL-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and indoleamine 2,3-dioxygenase (IDO) play the most important deleterious role on immune dysfunction observed in HIV infection[11-15]. Recently, the IDO-dependent tryptophan/kynurenine pathway has been recognized as a key factor contributing to HIV immune dysfunction, leading to distinctive damage to gut mucosa and brain tissue integrity[4,10,16]. Other viral infections associated with HIV, like herpes and CMV as well as hepatitis B and C, also further contribute to immune imbalance induced by an enhanced kynurenine pathway (KP), reviewed elsewhere[17]. This review focuses on the different factors involved in the establishment of the vicious cycle of the KP in the context of HIV infection that keeps the host in a state of chronic immune activation, with detrimental effects on several tissues and organs.

Kynurenine pathway: A crossroad between nutrition, microbes and host

The KP is the principal pathway to metabolize the essential amino acid tryptophan (Trp) in peripheral tissues, including skeletal muscle, liver, and white blood cells, leading to the production of blood-brain barrier-penetrating kynurenine (Kyn)[18]. The KP is also involved in protein synthesis of tryptamine as well as serotonin and melatonin synthesis (Fig. 1)[19,20]. Both IDO-1 and its paralogue IDO-2 are dioxygenase enzymes present in DCs and macrophages, which break down Trp into a series of catabolites, most importantly Kyn[19-21]. One of the end products of the KP is nicotinamide adenine dinucleotide, which plays an important physiological role in cellular functions as a co-factor[19]. Recent work has uncovered the KP as a key regulator of the energy production, protein synthesis, mood regulation, and systemic tolerance and immune privileged sites including the feto-maternal interphase[13,17,22].

The Kyn metabolism is double-edged sword; it acts on microorganisms to both inhibit growth during acute infections and to induce immunosuppressive effects in chronic infections. This pathway seems to constitute a delicate balance between pathogen defense and host protection. Since 1984, anti-proliferative features of IDO on bacterial and protozoan infections have been reported[17,23]. The expression of IDO in antigen-presenting cells induced by exogenous pathogens can limit intracellular bacterial infection through Trp starvation, as many of these microbial organisms are natural Trp auxotrophs, meaning they cannot synthesize their own Trp[24,25]. In addition to Trp depletion, production of Trp metabolites with bactericidal activity, such as Kyn, was also identified in human macrophages upon infection, which adds to the defense benefit mediated by IDO[20,26,27]. This starvation strategy has been proven to be effective in *Chlamydia pneumoniae* and *Listeria monocytogenes*[17]. However, this strategy may work less effectively for vacuolar organisms, such as *Legionella*, that do not have ready access to the cytoplasm, or for those with their own ability to synthesize Trp such as *Mycobacterium tuberculosis*[25]. The Trp depletion also plays a role in control of acute viral infections such as CMV, herpes simplex virus type 2[28] and measles[29]. On the other hand, IDO also has an impact on host cells to restrain immune reactions to avoid overwhelming immune damage, which promotes infection persistence. Elevated KP ratio has been observed in many chronic infections such as HBV, HCV, Epstein-Barr virus, and HIV infection.

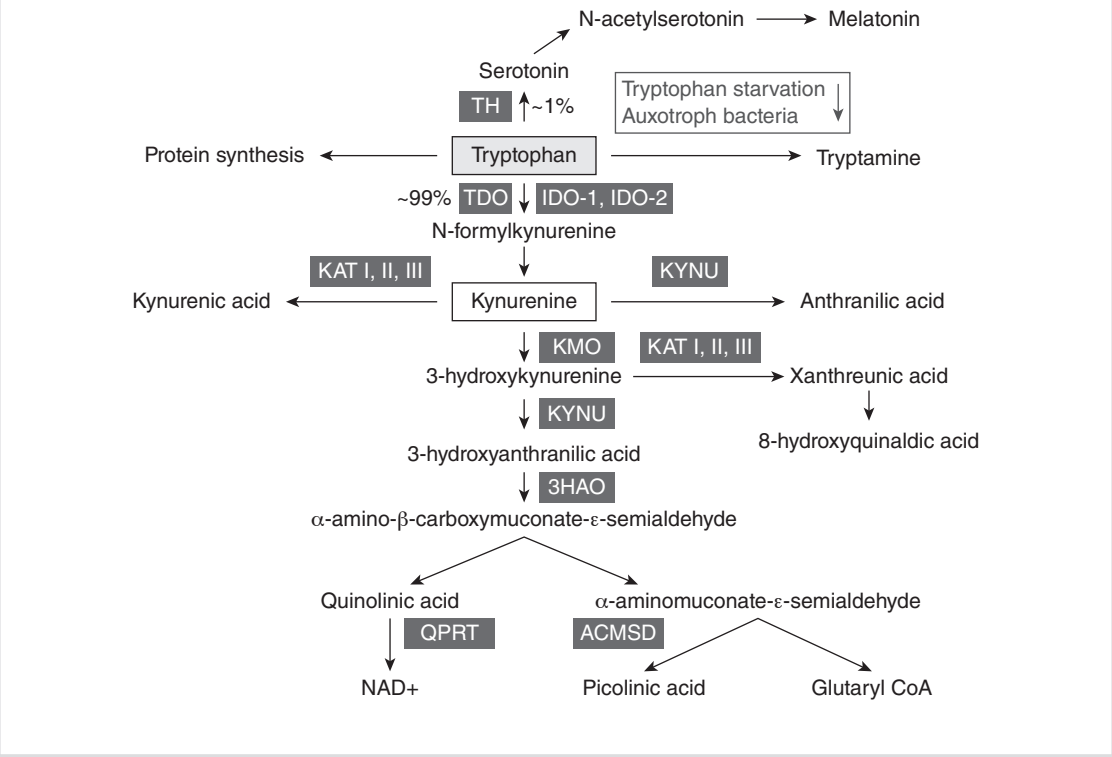

Figure 1. *Schematic representation of tryptophan and kynurenine metabolic pathway.*
TH: tryptophan hydroxylase; TDO: tryptophan 2,3-dioxygenase; IDO: indoleamine 2,3-dioxygenase; KAT: kynurenine aminotransferase; KYNU: kynureninase; KMO; kynurenine 3-monooxygenase; 3HAO: 3-hydroxyanthranilic acid oxygenase; QPRT: quinolinate phosphoribosyltransferase; ACMSD: α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase.

Recent focuses on the gut microbiota have found an important link between IDO metabolism and the gut microbial sensor aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor. AhR was found to feedback with IDO and Kyn to maintain a state of immune tolerance between commensal microbiota and the host[30,31]. The IDO is induced by IFN-γ in response to inflammatory signals[32] and its catabolites regulate immune homeostasis by acting as AhR ligands, allowing the generation of T regulatory (T_{reg}) cells[33,34]. In addition, tryptophan 2,3-dioxygenase (TDO), a hepatic enzyme highly similar to IDO, also induces Trp degradation along the KP[19,35]. The TDO can be induced by cyclic adenosine monophosphate-dependent hormonal stimulation, mainly in the liver but also in placenta, testis, and brain as well as in cancer cells[36,37] (Fig. 2).

During the last decade, a wealth of information indicates that enhanced immunosuppressive Kyn production by IDO and/or TDO plays a harmful role in cancers, different neurological conditions, and chronic viral infections including HIV infection[10,14,38]. Kyn inhibits T-cell proliferation[39,40], while another IDO catabolite, quinolinic acid, damages brain tissue contributing to AIDS dementia[41]. It is well established that monocyte-derived DCs specifically expressing IDO promote T_{reg} expansion[42,43] and contribute to the control of a hyperinflammatory state. Increased plasma Kyn levels and Kyn/Trp ratios represent a negative predictor of clinical outcome and have been found in patients with different inflammatory conditions and sepsis[44]. The importance of the KP has been recently recognized due to the better understanding of the complex relationship between the Th17/Th22/T_{reg} balance, gut microbiota composition, and microbial translocation. The KP may be considered as a double-edged sword as it is both initially helpful, but harmful long-term. During acute infection, the KP is part of an endotoxin tolerance defense pathway to prevent an exaggerated immune

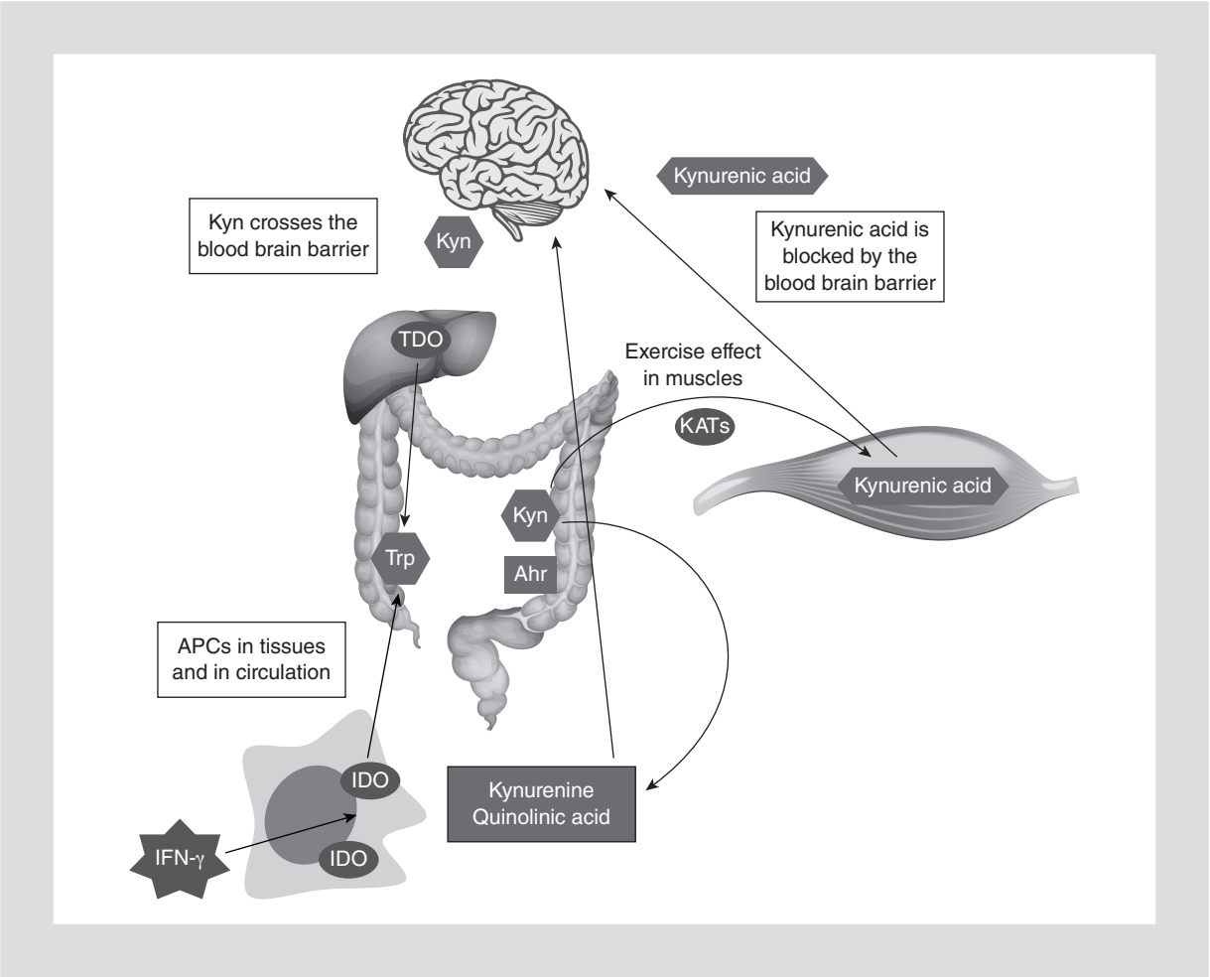

Figure 2. *Overview of major steps in kynurenine pathway. Antigen-presenting cells produce indoleamine 2,3-dioxygenase -1 and -2 with increased amounts under inflammatory cytokines such as interferon-g, while tryptophan 2,3-dioxygenase is produced in the liver. These enzymes catabolize tryptophan coming from gut via circulation into kynurenine, which also forms a feedback loop with aryl hydrocarbon receptor. Kynurenine enters the blood stream and along with its catabolites, such as quinolinic acid, crosses blood brain barrier to reach the brain. Exercise leads to production of kynurenine aminotransferases, which metabolize kynurenine into non-brain penetrating kynurenic acid.*
APC: antigen presenting cell; Trp: tryptophan; Kyn: kynurenine; Ahr: aryl hydrocarbon receptor; KAT: kynurenine aminotransferase; TDO: tryptophan 2,3-dioxygenase; IDO: indoleamine 2,3-dioxygenase.

response. However, during chronic infection the KP participates in the induction of an immune tolerance/exhaustion status that prevents tissue damage but surrenders the immune system to the microbial infection[31]. In HIV infection, the KP creates a self-sustaining feedback loop, which constitutes a vicious cycle of immune activation combining viral and bacterial factors.

Kynurenine pathway during HIV disease progression and impact of antiretroviral therapy

The link with increased KP and HIV infection was first established in 1998 by Huengsberg, et al. reporting on the elevation of Kyn/Trp ratio when compared to control individuals in a group of 206 HIV-infected patients[45]. A strong association between the Kyn/Trp ratio, CD4 T-cell counts, and the stage of the disease has been observed. The median Kyn/Trp ratio for asymptomatic and AIDS patients was two and three folds higher, respectively, than controls. The authors concluded that elevated Kyn/Trp ratio could lead to accumulation of quinolinic acid that in turn may be a contributor to AIDS dementia pathogenesis. Four years later, Zangerle, et al. prospectively assessed the contribution of ART to improving the KP. After six months of therapy, the Kyn/Trp ratio decreased by more than twofold[46]. Interestingly, Kyn/Trp ratios positively correlated with neopterin, a macrophage-derived proinflammatory marker, plasma virus load, and CD4 T-cell counts. Byakwaga, et al. later reported on

435 advanced HIV patients from Uganda who initiated ART and were assessed for Kyn/Trp ratio at month 6 and 12. A 46% decrease was observed at month 6 with a further decrease of 15 % at month 12[47]. Interestingly, due to a large participation of female patients, the authors observed a higher plasma Kyn/Trp ratio in women than men. Chen, et al. also showed a decrease in Kyn/Trp ratio without normalization after one year of ART in advanced patients from China[48]. Our group reported that long-term, successfully ART-treated patients had similar Kyn/Trp ratios to their aged-matched controls[10]. Collectively, these study findings summarized in table 1 indicate that Kyn/Trp ratios were consistently linked to CD4 T-cell counts, level of T-cell activation, and viral load, making it tempting to assess the KP as a new marker for HIV disease progression (Table 1).

Kynurenine pathway as a new independent marker for HIV disease progression

Predictor of mortality

Byakawaga, et al.'s Ugandan cohort was also assessed for markers of mortality[47]. Patients were advanced in their infection, with a mean CD4 T-cell count of 133/mm^3, mean viral load of 5.0 log copies/ml and a very elevated Kyn/Trp ratio before initiating ART. After adjustment for baseline CD4 T-cell counts, viral load, body mass index, and age, higher Kyn/Trp ratios independently predicted a lower CD4 T-cell recovery and increased mortality. The same group of investigators also reported on the predictive value of Kyn/Trp ratio on mortality in US patients receiving ART[4]. By using a case-control study among the 192 patients from well-established cohorts of patients, Hunt, et al. showed that Kyn/Trp ratio was an independent predictor for mortality along with other soluble factors of inflammation such as interleukin (IL)-6, C-reactive protein (CRP) and D-dimer. Conversely to their prior study on untreated Ugandan patients, CD4 and CD8 T-cell activation and exhaustion markers were not predictors of mortality for patients receiving ART[4].

Predictors of non-AIDS events related to inflammation

Despite the major influence of ART on patient survival, complications remain more frequent in HIV-infected patients than aged matched noninfected adults. Markers of immune activation and inflammation have been previously identified as predictors for non-AIDS events independently of other cardiovascular risk factors[49,50]. However, the contribution of the KP predictive values on development of non-AIDS events has not been previously assessed. To this end, Tenorio, et al. conducted a case-controlled study of HIV-infected patients who were successfully treated with ART[2]. After controlling for confounders, Kyn/Trp ratio along with IL-6, soluble tumor necrosis factor receptor, and D-dimers were the only markers associated with non-AIDS events when measured one year after ART initiation. Importantly, study findings indicate that in the context of ART, T-cell markers of activation and exhaustion were not predictors of non-AIDS events. Serroana-Villar, et al. identified the contribution of the CD4/CD8 ratio on morbidity and mortality in a cohort of 192 ART-treated patients and were able to show that such an association was driven by the heightened CD8 T-cell count, even for patients having a satisfactory CD4 T-cell recovery exceeding 500 cells/mm^3 [51]. As expected from previous studies, the CD4/CD8 ratio was inversely associated with levels of markers of innate immune activation like IL-6, CRP, sCD14, and Kyn/Trp ratio[52-54]. Interestingly, for the 49 patients having more than 500 CD4 T-cells/mm^3, such associations with CD4/CD8 ratio were lost for all the innate markers with the exception of Kyn/Trp ratio, using a multivariate linear regression analysis. Furthermore, the Kyn/Trp ratio had the strongest association for predicting non-AIDS events when compared to IL-6, sCD14, with intestinal fatty acid binding protein and zonulin, two markers of gut epithelial integrity. The Kyn/Trp ratio was the only innate immune marker, which remained associated with gut integrity markers in patients with more than 500 cells/mm^3 [51]. In all these studies, predictors for both mortality and morbidity for ART-treated patients were related with myeloid cell soluble factors like IL-6, sCD14, D-Dimer, and Kyn/Trp ratio. Collectively, these studies represent a paradigm shift as lymphoid markers of immune activation are no more predictors for both mortality and morbidity, while myeloid cell inflammation markers have become predictors for patients receiving long-term ART. However, mechanistic studies are needed to determine the direct contribution of the KP on clinical outcome in HIV infection.

Players involved in the creation of the kynurenine pathway cycle during HIV infection

HIV infection is associated with T-cell dysfunction characterized by a reduced CD4 T-cell count, impaired proliferative capacity of T-cells accompanied by an IDO/AhR dependent induction of T_{regs}.

Table 1. Studies reporting the effect of antiretroviral therapy on indoleamine 2,3-dioxygenase activity

Reference	Study site	Demographics	ART treatment	Average duration of treatment	Duration of follow-up	CD4 T-cell count	Viral load	IDO activity (KYN/TRP)	Comments
Huengsberg, et al.[45]	Birmingham and London, UK	n = 296* Patients: 206 – Majority male Control: 72 – Male: 72 (100%)	53 on AZT 23 on didanosine or zalcitabine	NA for a group of patients 1-12 months range of AZT therapy	240.5 days	Pre-treatment – Mean: 287/mm^3 Post-treatment – Mean: 229/mm^3	NA	Median ratio 67.3 before and 59.1 after AZT (n = 15; p = 0.05)	15 patients on AZT were analyzed for Kyn/Trp ratio pre- and post-treatment
Zangerle, et al.[46]	Innsbruck, Austria	n = 86 Patients: 45 – Mean age: 37 – Female: 15 (33%) – Male: 30 (67%) Controls: 40 – Mean age: 42 – Female: 20 (50%) – Male: 20 (50%)	(A) 11 on 2 NRTI (B) 18 on 2 NRTI + 1 PI (C) 5 on 2 NRTI +1 NNRTI (D) 11 on 2 NRTI +1 NNRTI +1 PI	6 months	6 months	Median CD4 cell count: 112 /ul At 6 months 232 cells/ul (p = 0.001)	Baseline median HIV RNA: 5.38 log10 copies/ml During the study fell below 400 copies/ml in 34 patients (75.5%)	Pre-treatment: 79.2 mmol/mol At 6 months: 19.1 mmol/mol (28.1% decrease)	Tryptophan degradation increased in HIV infection, triggered by immune activation and partially reversed under ART
Jenabian, et al.[10]	Montreal, Canada	n = 253 Naive: 96 ST: 88 EC: 19 HS: 50	NA	8.1 years in ST	ST on ART since 8 years	Mean cells/µl Naive: 416 ST: 531 EC: 618 HS: 813	Mean log10 copies/ml Naive: 4.0 ST < 1.6 EC < 1.6	ART naive: 0.054 ST: 0.041 EC: 0.039 HS: 0.033	Kyn/Trp ratio elevated in ART-naive subjects compared to all other groups
Byakwaga, et al.[47]	Mbarara, Uganda	n = 435 Median age 34 Male: 130 (30%) Female: 305 (70%)	2 NRTI + 1 NNRTI	6 months 12 months	1 year Kyn/Trp ratio assessed at months 6 and 12	Median: 133 cells/mm^3	Pre-treatment: 5.0 log 10 copies/ml 6 and 12 months < 400 copies/ml	Before ART, median plasma Kyn/Trp ratio: 130 nM/µM At month 6, 72 nM/µM 46% decrease At months 12 62 nM/µM 15% further decrease from 6 month ratio	Higher pre-ART Kyn/Trp ratio associated with higher plasma viral load (p < 0.001) and LPS (p = 0.018), lower CD4+ T-cell count (p < 0.001), and female sex (p = 0.047)
Chen, et al.[48]	Shanghai, China	n = 92 Patients: 76 – Median age: 32 – Male: 58 (76%) – Female: 18 (24%) Controls: 16 – Median age: 32 – Male: 10 (63%) – Female: 6 (37%)	73 on 2 NRTI + 1 NNRTI 3 on 2 NRTI + 1 PI	1 year	1 year	Baseline – Median: 248 cells/mm^3 Post ART – Median: 332.5 cells/mm^3	Undetectable < 40 copies/ml in 72 patients	Before ART elevated in patients (59.43 vs. 38.25 nM/mM) p < 0.0001 Reduces post ART to 42.43 nM/mM, (p = 0.0025), but still not normalized (p = 0.0148)	IDO activity significantly reduced post treatment but not normalized

(Continue)

Table 1. Studies reporting the effect of antiretroviral therapy on indoleamine 2,3-dioxygenase activity *(continued)*

Reference	Study site	Demographics	ART treatment	Average duration of treatment	Duration of follow-up	CD4 T-cell count	Viral load	IDO activity (KYN/TRP)	Comments
Page, et al. J Acquir Immune Defic Syndr. 2014	London, UK	n = 52 Controls: 16 – Mean age: 40.5 – Female: 1 (6%) – Male: 15 (94%) HIV ART: 16 – Mean age: 47.7 – Female: 0 (0%) – Male: 16 (100%) HIV naive: 20 – Mean age: 40.3 – Female: 4 (20%) – Male: 16 (80%)	HIV ART: 16 HIV naive: 20 Details NA	HIV ART, median 8 years	Not available Cross-sectional study	Controls – Median: 777 cells/µl HIV ART – Median: 619 cells/µl HIV naive – Median: 283 cells/µl	Controls: NA HIV ART – Median: 50 copies/ml HIV naive – Median: 85,505 copies/ml	Median Kyn/Trp (nM/uM) HIV naive vs. controls: 72.0 vs. 39.4; p < 0.0001 HIV naive vs. HIV ART: 72.0 vs. 46.6; p < 0.0015	Increased IDO activity inversely correlated with Th22:Treg and Th17:Treg ratios in ART-naive group

*Complete demographic information missing.
AZT: zidovudine; Kyn/Trp: kynurenine/tryptophan ratio; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Naive: untreated ART-naive patients; ST: ART successfully treated; EC: elite controllers; HS: healthy subjects; NA: not applicable; LPS: lipopolysaccharide.

HIV proteins Tat and Nef

Knowing that quinolinic acid acts as a neurotoxic product of the KP and has been shown to be elevated in the cerebrospinal fluid of patients with AIDS dementia, Smith, et al. first reported on the direct effects of HIV viral proteins Tat and Nef on the induction of human macrophages. They showed that both Tat and Nef were able to induce IDO and quinolinic acid production by macrophages[55]. In treated infections, very low levels of viral replication including Tat production can still contribute to IDO induction in macrophages and DCs[56].

The virus and its main inflammatory pathway, interferon-γ

In HIV infection, elevation of plasma levels of INF-γ and IDO mRNA in peripheral blood mononuclear cells (PBMC) points toward the involvement of IDO in T-cell dysfunction[57,58]. Although it is well established that INF-γ is a strong inducer of IDO, it remains difficult to determine whether it is a cause or effect. *In vitro* infection of PBMCs leads to the secretion of INF-α and INF-β by plasmacytoid DCs, that in turn leads to an INF-γ induction. The recent findings on the contribution of composition of the microbiota and microbial gut translocation in HIV infection have made the interactions between IDO and INF-γ even more complex. IDO causes alterations to the Th17/Th22/T_{reg} balance in the gut mucosa, leading to microbial translocation. In 2010, Favre, et al. linked the KP with the decrease in a functional subset of CD4 T-cells secreting IL-17 (Th17) and the increase of T_{regs} in both blood and in rectal mucosal tissues in HIV-infected patients[14]. By using *in vitro* activation assays in the presence of varying concentrations of Trp catabolites, the investigators were able to modulate the balance of Th17 and T_{regs}. The loss of the mucosa protector Th17 population was associated with induction of IDO by myeloid DCs and with increased plasma concentration of microbial products. They were also able to show that this deleterious effect on Th17/T_{reg} balance was mediated by 3-hydroxyanthranilic acid, a proximal downstream Trp catabolite of IDO-1. Collectively, these data support a model by which persistent activation of IDO-1 diminished the host capacity to maintain protective Th17 cells and favor the generation of immunosuppressive T_{regs}[59]. The consequence of this imbalance is a progressive loss of the mucosal epithelial barrier, leading to an increased microbial translocation[60]. The systemic circulation of microbial products will in turn fuel myeloid

cell activation by their toll-like receptors, creating a vicious cycle of induction of the KP, which further induces immunosuppression and a chronic state of inflammation[61].

Kynurenine pathway induction and composition of gut microbiota

Several studies have linked HIV to changes in the gut microbiota. Vujkovic-Cvijin, et al. showed that HIV-infected viremic patients had microbiota communities enriched in Proteobacteria, most notably of the family *Enterobacteriaceae*, which includes known pathological microbes such as *Salmonella*, *Escherichia* and *Shigella,* and depletions in *Bacteroides* and *Alistipes*[62]. The changes to the microbiota composition from these patients were linked to a decrease in Th17 cells in gut biopsies as well as an increase in Kyn/Trp ratios and IFN-γ-induced protein-10, an INF-dependent cytokine[62]. The IDO activity and the microbiota post-infection appear to create a positive feedback loop, favoring growth of pathogens. Most importantly, bacteria enriched in viremic patients possess enzymatic homologs of IDO capable of local production of Kyn from Trp. Such newly invading bacterial communities can out-compete the normal constituents of the microbiota due to Kyn production through IDO and, once established, capable of producing Kyn to further fuel their growth. Partial reparation of the gut mucosa and enriched lactobacilli in the gut microbial composition was reported by Perez-Santiago, et al. following ART initiation[63]. As in both healthy and HIV-infected patients, *Lactobacilli* contribute to the maintenance of physiological gut immunity. Zelante, et al. further explored their interplay with the KP using a mouse model[64]. They found that *Lactobacilli* are capable of catabolizing Trp into indole-3-aldehyde and in turn able to stimulating natural killer cells via AhR to produce IL-22, which controls the gut microbiota, ensuring a diverse ecosystem. Accumulating information from animal and human research also strengthens the concept of the importance of the KP in the microbiota-gut-brain axis[65].

Kynurenine pathway and neurological impairment in HIV infection

HIV directly infects myeloid-derived cells in the central nervous system, resulting in cognitive impairment and, in absence of ART, can lead to dementia[66]. As these two conditions intertwine, they are now designated by the term “HIV-associated neurocognitive disorder” (HAND). Aging patients receiving ART have higher burdens of neurological disorders compared to HIV-noninfected controls[67]. From *in vitro* and *in vivo* data, the KP has been implicated in the pathogenesis of HAND. The contribution of Trp and Kyn has been thoroughly reviewed in brain tumors and psychiatric disorders and are associated with a reduction of serotonin (5-HT) and serotonin transporter (5-HHT) expression, as well as an accumulation of other Trp metabolites (Fig. 1)[68,69]. Two Trp metabolites, Kyn and quinolinic acid, can be detected in the cerebrospinal fluid of HIV-infected patients and correlate with the severity of HAND[70,71]. Furthermore, high Kyn/Trp ratio in patients is associated with severity of depression, but the ratio can be reversed with ART[72]. Conversely, physical activity causes conversion of Kyn to kynurenic acid in the muscles via kynurenine aminotransferases. Once in the blood stream, kynurenic acid, unlike Kyn, cannot breach the blood brain barrier, thus causing physical activity to act as an antidepressant in mouse models[73]. The mechanisms by which the KP directly participates in HAND has been mainly based on animal models and has been recently reviewed[66].

Breaking the kynurenine pathway to improve patient outcomes

Interventions to reduce the KP cycle should include direct IDO inhibitors and factors contributing to its induction like gut microbiota composition and gut epithelial damage. The function of TDO, mainly expressed in the liver or brain, can also be inhibited to decrease the KP. As the ligation of Kyn to AhR can allow the direct generation of T_{reg} cells, AhR may also represent a newly identified target for therapy[34].

IDO and TDO inhibition

1-methyl-tryptophan (1-MT), a competitive inhibitor of IDO, induces a transitory neurological protection after lipopolysaccharide challenge in chemo-attractant cytokine CX3CL1-/- deficient mice[74]. In another mouse model, 1-MT was able to reduce the number of HIV-infected brain macrophages by 90%[75]. However, disappointing results were reported with 1-MT when used in SIV-infected rhesus macaques on ART[76,77].

New IDO inhibitors are under development as anticancer therapies and some are assessed in clinical trials including indoximod combined with chemotherapy[78-82]. A recent review has summarized current and future drug discovery landscape targeting dioxygenases[83].

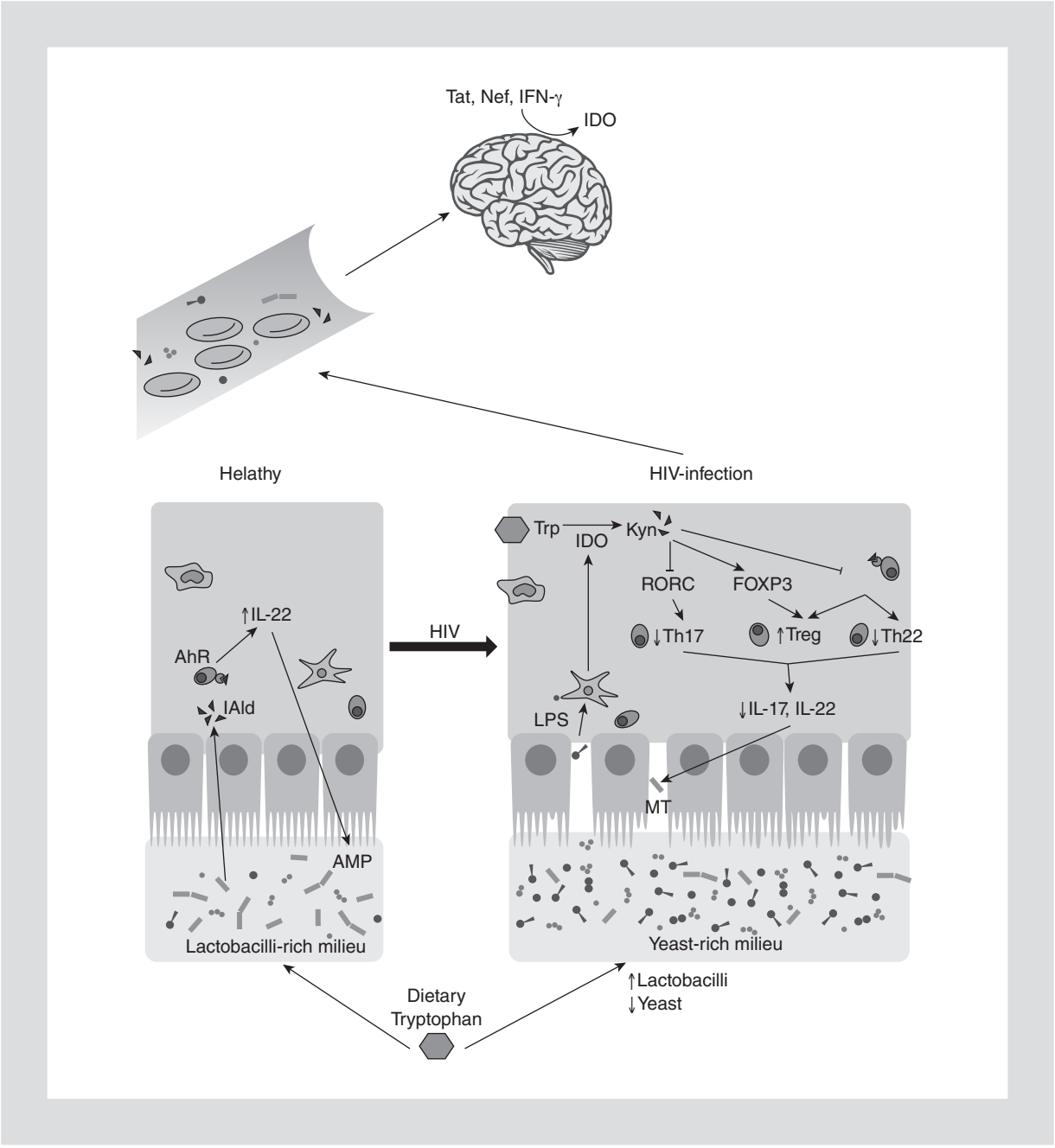

Figure 3. *Kynurenine pathway in the digestive mucosa. In a healthy state, the microbiota interacts with the immune system to create immune balance and microbial control. After HIV-infection, the microbiota shifts in composition, which creates microbial translocation and indoleamine 2,3-dioxygenase activation. The indoleamine 2,3-dioxygenase leads to an imbalance of immune cells as microbial and kynurenine pathway products enter the blood stream, and eventually the brain causing serious downstream events.*
KP: kynurenine pathway; IDO: indoleamine 2,3-dioxygenase; AhR: Ahr: aryl hydrocarbon receptor; AMP: antimicrobial peptides; IAID: indole derivative; IL: interleukin; Kyn: kynurenine; MT: microbial translocation; Trp: tryptophan.

Combining non-redundant key immune-metabolic pathways

Recently, reports on melanoma and brain tumors in mice showed that the combination of a new IDO inhibitors with either blockade of PD-1/PDL-1 or CTLA-4 were able to restore cytotoxic CD8 T-cell function in the tumor microenvironment, leading to an increase in survival[84,85]. Such non-redundant combined therapeutic approaches may have very important significance for the control of HIV inflammation as very common immuno-metabolic pathways are shared between cancers and HIV infection[86].

Concluding remarks

As part of the "extended self," commensal microbiota and its regulation by factors such as the KP play an important role in local gut mucosa immune tolerance as well as systemic control of immune activation in the host (Fig. 3).

The key role of the KP in HIV infection on immune dysfunction and neurocognition pave the way for strategies to modulate this immune-metabolic pathway, likely in combination with other immune inhibitory pathways like PD-1, or CTLA-4. Collaborative efforts between oncology, infectious diseases, and immunology will soon establish the clinical benefit of modulation of the KP[87].

Acknowledgements

The authors acknowledge Angie Massicotte for coordination and assistance. This work was supported by the Canadian Institutes of Health Research (grant MOP #103230 and the CIHR Canadian HIV Trials Network CIHR/CTN #257), the Canadian HIV Cure Enterprise (CanCURE), Fonds de la Recherche Québec-Santé (FRQ-S): Thérapie cellulaire and Réseau SIDA/Maladies infectieuses, Québec, Canada and the Canadian Foundation for AIDS Research (CANFAR) grant 023-512. We also acknowledge Jacquie Sas and Jim Pankovich for coordinating the research with the support of CIHR/CTN. Dr. Wei Cao is supported by the CTN International Postdoctoral Fellowship Award. Dr. Jean-Pierre Routy is the holder of Louis Lowenstein Chair in Hematology & Oncology, McGill University.

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