Tryptophan depletion and HIV infection: a metabolic link to pathogenesis

Michael F Murray

HIV-1-infected patients have low circulating tryptophan concentrations despite evidence of adequate dietary intake of this essential amino acid. A chronic increase in inducible tryptophan oxidation is the basis of HIV-1-associated tryptophan depletion. This metabolic process results in the irreversible loss of tryptophan molecules from the available pool. Such sustained disruption of normal tryptophan metabolism over time disturbs the many metabolic processes involving this amino acid, and has been implicated in some features of AIDS pathogenesis. Normal T-cell function is adversely affected by tryptophan depletion, but the extent of the effect in HIV-1-infected patients is still unclear. Attempting to directly supplement tryptophan is not advised given the potential increase in circulating concentrations of neurotoxic intermediates. Although only preliminary data are available, evidence suggests that antiretroviral and nicotinamide treatments can boost plasma tryptophan concentrations in HIV-1-infected patients and impact the secondary effects of tryptophan depletion. Additional study of this metabolism could lead to improved treatment strategies for patients with HIV infection. In this review I focus on the potential links between disturbed tryptophan metabolism and pathogenesis.

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Human beings cannot synthesise the indole ring of tryptophan (figure 1). The body’s supply of tryptophan, therefore, must be obtained from the environment in the preformed state. This dietary requirement places tryptophan in the group of essential amino acids. The required minimum daily intake for tryptophan is 175 mg daily for adult women and 250 mg daily for adult men. The average diet in developed countries far exceeds this requirement, generally including about 1 g tryptophan daily. Circulating concentrations of plasma tryptophan come from two sources: newly acquired dietary tryptophan, and tryptophan that has been released for recycling during protein turnover. HIV-1-infected individuals have no consistent dietary deficiency in proteins or amino acids, yet the plasma of patients with asymptomatic early disease and those with more advanced disease have a reproducible pattern of tryptophan depletion at all stages of infection (table 1). This depletion of tryptophan deepens with advancing disease, and contributes to HIV pathogenesis.

L-Tryptophan 2,3-dioxygenase (TDO) is the liver-specific enzyme that does most tryptophan oxidation via indole-ring cleavage during periods of homeostasis (figure 2A). Because of the high Km of TDO, it has notable activity only when tryptophan concentrations exceed basal requirements for protein and serotonin synthesis. Tryptophan, like other amino acids, can be oxidised to generate energy. Excess dietary tryptophan is routinely metabolised via this major oxidation pathway to produce ATP, carbon dioxide, and water in healthy adults. A side product of this metabolism is the production of niacin (ie, nicotinamide and nicotinic acid); in fact, the basal activity of this pathway transforms around 2% of dietary tryptophan molecules to niacin (figure 3). When tryptophan overload is experimentally induced (tryptophan load testing), up to 99% of the tryptophan is oxidised via TDO.

Inducible tryptophan oxidation can be initiated extrahepatically via a second enzyme, indolamine 2,3-dioxygenase (IDO). IDO was first isolated from rabbit intestine, and its in-vitro activity extends to indoleamine 2,3-dioxygenase in the periphery. Once cleaved, the indole ring cannot be resynthesised by human metabolism; any additionally required tryptophan must be obtained via dietary intake.

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containing compounds other than tryptophan.20 This enzyme is expressed in several cells, including macrophages, dendritic cells, and placental trophoblasts. It has been implicated in the overactivation of tryptophan catabolism in HIV-1 infection. Tryptophan concentrations were diminished by an average of 28·5% compared with controls (table 1).21,11,15–18 The rise of metabolic intermediates such as kynurenine and quinolinic acid implicates the tryptophan-oxidation pathway and not other potential explanations for tryptophan loss in HIV-1 infection. Just as there are tissue differences in IDO production, so there is substantial variability in the capacity of different tissues to provide the necessary enzymes for the other major steps in the main oxidation pathway.21

Two critical steps exist in the main tryptophan oxidation pathway. First, the initial and rate-limiting step in tryptophan oxidation is activated by TDO or IDO and is the irreversible cleavage of the indole ring (figure 1). Once tryptophan is removed from the body’s pool via oxidation it is no longer available for the other important uses, including its incorporation into proteins, and the minor oxidation pathway for the synthesis of serotonin and melatonin. In healthy adults, higher metabolic priority is given to tryptophan’s incorporation into proteins than to the conversion to niacin when the diet is experimentally manipulated.22 There is some evidence that limited tryptophan in HIV-1-infected patients does not limit protein synthesis.15 However, in HIV-1 infection, niacin is given metabolic priority over metabolic products such as serotonin (figure 2B).23,24

The second critical step is the conversion of aminocarboxymuconic semialdehyde to aminomuconic semialdehyde or quinolinic acid (figure 3). At this branch point, the fate of the carbon backbone is decided, taking the pathway towards niacin or that towards further oxidation. Picolinic carboxylase is the rate-limiting enzyme at this metabolic branch point. The oxidative conversion occurs preferentially, accounting for more than 90% of the end-product production. However, when picolinic carboxylase activity is limiting, a non-enzymatic reaction commits the molecule to the synthesis of niacin compounds.1 In normal individuals, only 1–2% of total tryptophan intake is shunted down the non-enzymatic path to niacin. In HIV-1-infected people, circulating niacin concentrations increase proportionately to the decrease in circulating tryptophan (figure 2A and 2B).25,26

Figure 2. Basal metabolism of tryptophan in an uninfected person in nitrogen balance, and altered metabolism of tryptophan in an HIV-1-infected person. (A) Daily protein synthesis requires three and a half times as much tryptophan as the total dietary intake. This requirement is achieved by use of a half times as much tryptophan as the total dietary intake. This requirement is achieved by use of dietary tryptophan and tryptophan recycled from protein degradation. The minor oxidative pathway for tryptophan to form serotonin and melatonin accounts for around 1% of total dietary intake. Niacin production accounts for around 5% of total tryptophan intake, and occurs as a side reaction in the major oxidative pathway. Most of the remaining dietary tryptophan is oxidised to create ATP, water, and carbon dioxide, or lost as urinary intermediates. Excess tryptophan is shunted down the major oxidative pathway via the hepatic enzyme TDO. (B) After infection protein turnover increases, but protein synthesis reaches a relative steady state as virus production reaches set point. Available tryptophan is shunted away from the minor oxidative metabolic pathway and out of the available pool into the inducible tryptophan oxidative pathway. This oxidation, at low concentrations, occurs extrahepatically via the enzyme IDO. Resting energy expenditure is increased in HIV-1-infected individuals, which necessitates increased ATP production, yet the amount of ATP via this pathway has not been measured. ACSMA=aminocarboxymuconic semialdehyde.
further study is needed to fully understand the complex relations between tryptophan and HIV-1 infection, this review focuses on the potential links between disturbed tryptophan metabolism and pathogenesis.

Biological stimuli underlying inducible tryptophan oxidation

Cytokines

Cytokines stimulate IDO expression and activity. Although interferons α and β, tumour necrosis factor α, and platelet-activating factor can induce tryptophan oxidation, interferon γ seems to be the most important cytokine linked to this catabolism. Induction of IDO can promote the removal of tryptophan in a localised microenvironment or systemically. Tryptophan oxidation driven by interferon γ can take place even when the circulating concentration of tryptophan is already low because of the relatively lower Km of IDO than that of TDO. Two concepts, applied separately, have been used to explain the removal of tryptophan via the host immune system: microbial aminoacid deprivation and immune tolerance. The fact that interferon γ induces a coordinated response within the cell that includes increased tryptophanyl-tRNA synthetase suggests that the cell prepares to meet the effects of the changes in tryptophan concentration on translation. Interferon γ increases IDO expression to induce the rate-limiting step in tryptophan oxidation, but does not seem to affect other enzymes in the oxidative pathway such as kynurenine, 3-hydroxylation, and 3-OH-kynureninase.

Non-viral infection

Non-viral intracellular pathogens, such as Toxoplasma gondii and Chlamydia psittaci, stimulate an interferon γ response and subsequent IDO-mediated tryptophan oxidation. In a mouse model of T gondii infection, the intraperitoneally injected protozoa localised to the lung and central nervous system (CNS) by 2 weeks, and detectable changes to the kynurenine:tryptophan ratio indicative of tryptophan oxidation were longest and most prominent in those organs. These observations, together with in-vitro studies of T gondii and Chlamydia sp, have led to the hypotheses that host tryptophan modulation, in the microenvironment of the infection, results in a competitive advantage for the host. The theory has been put forward that tryptophan depletion exists as a host strategy in these cases, aimed at decreasing microbial replication by starving intracellular parasites of tryptophan. Such a host strategy in localised intracellular infections may confer a host advantage, but a systemic depletion of an essential aminoacid as a host immune strategy would seem unsustainable over long periods of time since the host also requires the aminoacid and cannot resynthesise it.

![Figure 3. Availability of tryptophan. Available tryptophan can be used in one of three major pathways: (1) reversible incorporation into protein, (2) the minor oxidative pathway to serotonin and melatonin, and (3) oxidation for the production of energy and niacin compounds. Excess tryptophan induces the major oxidative pathway in the liver via TDO. Interferon γ, HIV-Tat, and HIV-Nef can all induce IDO to catalyse the initial rate-limiting step in tryptophan oxidation, irrespective of tryptophan concentrations at extrahepatic sites. The end products of oxidation are shown in blue. Tryptophan oxidation can increase glutamate (a) via increased alanine driving the conversion of α-ketoglutarate to glutamate. Lysine (b) and tryptophan partly share a common oxidative pathway, and excessive oxidation of either aminoacid may negatively feedback on the oxidation of the other. IFN=interferon. QPRT=quinolinate phosphoribosyl transferase.](http://infection.thelancet.com)
**Table 1. Studies examining plasma or serum tryptophan in HIV-1-infected patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tryptophan concentration</th>
<th>Intervention</th>
<th>Other measures</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werner et al., 1988</td>
<td>44.8 μmol/L in infected patients vs 91.0 μmol/L in controls</td>
<td>None specified</td>
<td>KT ratio 3/1 in patients vs controls</td>
<td>Increased KT ratio suggests increased tryptophan oxidation not dietary or other types of loss explain lower concentration</td>
</tr>
<tr>
<td>Larsson et al., 1989</td>
<td>28.4 μmol/L in infected patients vs 39.7 μmol/L in controls</td>
<td>No patients on antiretroviral medications</td>
<td>Cerebrospinal fluid tryptophan 1.52 μmol/L in infected patients vs 2.18 μmol/L in controls</td>
<td>Lower tryptophan concentrations most pronounced at low CD4 counts</td>
</tr>
<tr>
<td>Fuchs et al., 1990 (A)</td>
<td>48.8 μmol/L in infected patients with dementia or neuropsychopathy, 70.5 μmol/L in patients without dementia or neuropathy, and 91.1 μmol/L in controls</td>
<td>None specified</td>
<td>Neopterin concentrations have a reciprocal relation to tryptophan concentrations</td>
<td>Neurological findings correlated with lower tryptophan concentrations</td>
</tr>
<tr>
<td>Fuchs et al., 1990 (B)</td>
<td>29.8 μmol/L in infected patients vs 39.7 μmol/L in controls</td>
<td>None specified</td>
<td>Serum interferon-γ concentrations 159 U/L in patient serum vs 33 U/L in control serum</td>
<td>Inverse correlation between tryptophan and interferon-γ concentrations noted</td>
</tr>
<tr>
<td>Fuchs et al., 1991</td>
<td>57 μmol/L in infected patients vs 91 μmol/L in controls</td>
<td>38% of patients on zidovudine monotherapy</td>
<td>Interferon-γ 259 U/L in infected patients and 23.5 U/L in controls, kynurenine 3-45 μmol/L in infected patients vs 2.31 μmol/L in controls</td>
<td>p&lt;0.001 for inverse correlation between tryptophan and interferon-γ concentrations. No separate analysis based on antiviral therapy</td>
</tr>
<tr>
<td>Wiegand et al., 1991</td>
<td>45.0 μmol/L in patients with AIDS</td>
<td>28% on zidovudine monotherapy</td>
<td>Decreased plasma tryptophan associated with sleep disturbances</td>
<td>No separate analysis based on antiviral therapy</td>
</tr>
<tr>
<td>Heyes et al., 1992</td>
<td>40.2 μmol/L in infected patients vs 70.9 μmol/L in controls</td>
<td>No patients on antivirals</td>
<td>Tryptophan decreases accompanied proportional increases in kynurenine and quinolinic acid in serum and cerebrospinal fluid</td>
<td>Raised concentrations of neurotoxic intermediate quinolinic acid demonstrated.</td>
</tr>
<tr>
<td>Gisslen et al., 1994</td>
<td>29.4 μmol/L in infected patients pretreatment vs 36.2 μmol/L post-treatment</td>
<td>Zidovudine monotherapy for 3–14 months</td>
<td>No change in serotonin concentrations post-treatment.</td>
<td>Tryptophan increased 6.8 μmol/L (23%) post-treatment</td>
</tr>
<tr>
<td>Hortin et al., 1994</td>
<td>22 μmol/L in infected patients vs 46 μmol/L in controls</td>
<td>85% of patients on mono or dual nucleoside therapy</td>
<td>Decreased cysteine, tryptophan, methionine, increased taurine, lysine</td>
<td>Tryptophan and lysine showed trend of lower/higher with CD4 count &lt;200/μL. No separate analysis based on antiviral treatment</td>
</tr>
<tr>
<td>Brown RR, 1996</td>
<td>Tryptophan concentration in infected patients lower than controls, and lower in AIDS than in asymptomatic infection</td>
<td>None specified</td>
<td>Correlation between lower tryptophan and failure to thrive</td>
<td>Only paediatric patients studied</td>
</tr>
<tr>
<td>Eriksson et al., 1996</td>
<td>Tryptophan concentration 50% lower in infected patients than in controls</td>
<td>None specified</td>
<td>No change in concentration of other large neutral aminoacids (e, tyrosine, valine, phenylalanine, leucine, isoleucine)</td>
<td>Plasma ratios of tryptophan to other large neutral aminoacids predicted to affect active transport of tryptophan to CNS via shared transporter</td>
</tr>
<tr>
<td>Laurichesse et al., 1998</td>
<td>51 μmol/L in infected patients vs 59 μmol/L in controls</td>
<td>None specified</td>
<td>Five other essential aminoacid concentrations also depressed (methionine, threonine, histidine, isoleucine, leucine)</td>
<td>Despite lower concentrations, tryptophan does not seem to be rate limiting in protein synthesis in AIDS patients</td>
</tr>
<tr>
<td>Huingsberg et al., 1998</td>
<td>Tryptophan concentration 33.2 μmol/L in patients with AIDS, 50.1 μmol/L in people with asymptomatic HIV-1 infection, and 56.3 μmol/L in controls</td>
<td>None specified</td>
<td>Tryptophan concentration was 43.8 μmol/L in patients with CD4 less than 200, 44.0 μmol/L in patients with CD4 200–500, and 55.1 μmol/L in patients with CD4 greater than 500/μL.</td>
<td>KT ratio and kynurenine concentrations had reciprocal relation to tryptophan. Advanced HIV disease correlates with evidence of increased tryptophan oxidation</td>
</tr>
<tr>
<td>Look et al., 2000</td>
<td>44.6 μmol/L in infected patients pretreatment vs 53.0 μmol/L post-treatment</td>
<td>Individualised HAART regimens for 3 months</td>
<td>Tryptophan increased 8.4 μmol/L (19%) post-treatment</td>
<td></td>
</tr>
<tr>
<td>Murray et al., 2001</td>
<td>49.3 μmol/L in infected patients pretreatment vs 69.2 μmol/L post-treatment</td>
<td>Oral nicotinamide 3 g per day for 2 months. Patients were either on no antivirals or on a stable regimen for &gt;2 years.</td>
<td>The concentration of cysteine, methionine, taurine, and lysine remained unchanged by treatment. No separate analysis based on antiretroviral therapy</td>
<td>Tryptophan increased 19.9 μmol/L (40%) post-treatment</td>
</tr>
<tr>
<td>Zangerle et al., 2002</td>
<td>44.1 μmol/L in infected patients pretreatment vs 53.2 μmol/L post-treatment</td>
<td>Individualised HAART regimens for 6 months</td>
<td>Tryptophan increased 9.1 μmol/L (21%) post-treatment</td>
<td></td>
</tr>
</tbody>
</table>
Pregnancy

Pregnancy is associated with the stimulation of IDO. In mammals, survival of the fetus during pregnancy depends on tryptophan oxidation at the maternal-fetal interface. Increased tryptophan oxidation during pregnancy was first recognised 50 years ago, but its link to the immune response is a recent discovery. Oxidation occurs at the placenta, but this localised phenomenon is the apparent driving force for systemic tryptophan depletion in pregnancy. Pregnancy has long been known to induce a clinical state of relative immunodeficiency, particularly in cell-mediated responses, and this deficient response is attributable, at least partly, to systemic tryptophan depletion. A change in immune reactivity is required for tolerance of the paternal antigens presented by the hemiallogenic fetus. In fact, the failure to suppress T-cell proliferative responses in pregnancy seems to be associated with recurrent miscarriage in human beings. Since fetal cells and the paternal antigens they bear are present at the placental interface and in the maternal bloodstream (ie, fetal erythrocytes, lymphocytes, granulocytes, trophoblasts, and haemopoietic stem cells), systemic rather than simply localised immunotolerance is needed. At the end of pregnancy the state of systemic immune tolerance driven by tryptophan oxidation resolves.

HIV-1 proteins

In HIV-1 infection tryptophan oxidation is stimulated by specific viral antigens. This observation raises the possibility that the virus benefits from activation of this metabolism. HIV-Nef and HIV-Tat, but not HIV-gp41 or HIV-gp120, induce IDO expression and tryptophan oxidation. HIV-1 infection could have evolved mechanisms to initiate activation of this metabolic pathway to gain a competitive advantage over the host. In addition to effects on infected cells, HIV-Tat can be exported from infected cells and enter uninfected cells, so could potentially activate this pathway in a wide range of cell types. Another viral antigen with potential relevance to viral activation of this metabolic pathway is HIV-p17, a matrix protein that localises to the nucleus and shares structural and functional features with interferon γ. The specific question of whether HIV-p17’s shared functions extend to IDO activation has not been examined. The interactions of other primate retroviruses with tryptophan metabolism are less well defined. However, there are changes in tryptophan concentration in human T cell lymphotrophic virus 1 (HTLV-1) infection, and increases in tryptophan oxidation metabolites in simian immunodeficiency virus infection.

Biological consequences of tryptophan catabolism by IDO

T-cell hyporesponsiveness

T-cell response to foreign antigens is depressed in the peripheral blood of HIV-1-infected individuals and pregnant women. Increased IDO activity in HIV-1 infection results in decreased tryptophan and increased niacin, in a pattern reminiscent of human pregnancy (table 2). This pattern of tryptophan-to-niacin metabolism in pregnancy is critical to conferring immune tolerance of foreign paternal antigens. Cytokine-induced tryptophan oxidation has also been linked to the induction of tolerance of foreign antigens in other settings. Further study is required to find out whether this metabolic pattern is linked to tolerance of HIV antigens. This potential link is, however, supported by the observation that HIV-1-associated T-cell anergy can be induced by HIV-Tat, the same viral protein that induces IDO expression and tryptophan oxidation.

Changes in T-cell proliferation and viability

Tryptophan deprivation of T cells has also been linked to cell cycle arrest in G1 and cell death (table 2); these tryptophan-oxidation-associated phenomena could potentially contribute to the steady loss of circulating CD4 T lymphocytes, which is the hallmark of advancing disease in HIV-1 infection. In-vitro studies show that T-cell G1 arrest can be reversed only with tryptophan repletion and restimulation of the T cell receptor, an observation with potential implications for structured treatment interruptions in patients.

Table 2. Potential links between observed changes in HIV-1-infected patients and overactivation of inducible tryptophan oxidation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Observed change</th>
<th>Mechanism associated with tryptophan oxidation</th>
<th>Potential pathogenic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heyes et al, 1992</td>
<td>Raised quinolinic acid</td>
<td>Quinolinic acid is a metabolic intermediate of niacin coenzyme synthesis</td>
<td>Neurotoxic effects</td>
</tr>
<tr>
<td>Mellor and Munn, 2001</td>
<td>T-cell depletion</td>
<td>T-cell proliferation defect associated with low extracellular tryptophan concentrations</td>
<td>Cell-cycle arrest in G1 and AICD</td>
</tr>
<tr>
<td>Mellor and Munn, 2001</td>
<td>T-cell hyporesponsiveness</td>
<td>Defect in responsiveness to foreign antigen associated with low extracellular tryptophan concentrations</td>
<td>Immunotolerance</td>
</tr>
<tr>
<td>Launay et al, 1989, Wiegand et al, 1991</td>
<td>Decreased serotonin</td>
<td>Metabolic diversion from tryptophan’s hydroxylative to oxidative pathway</td>
<td>Mood and sleep disorders</td>
</tr>
<tr>
<td>Grunfeld and Feingold, 1992</td>
<td>Hypermetabolism/raised resting energy expenditure</td>
<td>Primary end products of tryptophan oxidation ATP, carbon dioxide, and water</td>
<td>Wasting</td>
</tr>
<tr>
<td>Ferrante et al, 2001</td>
<td>Increased glutamate</td>
<td>Tryptophan oxidation produces alanine, which converts a ketalglutamate to glutamate</td>
<td>Neurotoxic effects</td>
</tr>
</tbody>
</table>

AICD=activation-induced cell death.
**Quinolinic-acid production**

Quinolinic acid is a neurotoxic metabolic intermediate of tryptophan oxidation along the niacin subpath (figure 3). Localisation of IDO activity and increased quinolinic acid in the brain has been associated with HIV dementia (table 2). While the concentration of quinolinic acid is raised in the periphery and the CNS of HIV-1-infected individuals, the increase is proportionately higher in the CNS. Although IDO activity initiates the metabolism, there may be a tissue-specific decrease in picolinic carboxylase or quinolinate phosphoribosyl transferase activity in the CNS to account for the increased concentrations there (figure 3). Quinolinic acid's neurotoxic effects are believed to be mediated by its excitotoxic activation of N-methyl-D-aspartate (NMDA) receptors. The specific quinolinic-acid inhibitors have been discussed, but antiretrovirals that reduce extrahepatic tryptophan oxidation have proven effective in reducing quinolinic-acid concentrations clinically, thereby lowering the risk of dementia.

**Increased endogenous niacin**

Increased tryptophan oxidation leads to a net increase in circulating niacin (table 2). Such an increase has been documented in pregnancy and two infections associated with interferon—HIV and tuberculosis caused by *Mycobacterium tuberculosis*. Circulating niacin in these circumstances could have at least two potential effects. First, niacin might feedback to inhibit excessive tryptophan oxidation by IDO in the same way as niacin can inhibit TDO. Second, the availability of increased nicotinamide, the major circulating form of niacin, provides a precursor to cells for intercellular NAD production. In HIV-1 infection, intercellular NAD is decreased, putting infected and uninfected cells at risk of NAD-depleted cell death. Although NAD replenishment associated with tryptophan oxidation may be a host metabolic goal, this production of niacin via tryptophan oxidation comes at a significant energy cost, since the human body is inefficient at converting tryptophan to niacin.
Altered metabolic rate
The increase in the basal metabolic rate of HIV-1-infected people remains poorly explained.⁶¹,⁶² Resting energy expenditure is raised in all HIV-1-infected individuals, even if asymptomatic and with normal CD4 counts (table 2). Despite this increased resting energy expenditure, asymptomatic patients compensate and maintain normal bodyweights. A cytokine-driven mechanism, such as by tumour necrosis factor α, for increased resting energy expenditure has been suggested, yet studies have shown no correlation in HIV-1-infected people. Interferon γ as a stimulus for increased resting energy expenditure in HIV-1 infection has not been investigated. The tryptophan oxidation that HIV-Tat, HIV-Nef, and interferon γ drive results in energy production from a typically unavailable source—ie, in an individual in nitrogen balance tryptophan is not an energy source unless it is in excess. Therefore, extrahepatic tryptophan oxidation in HIV-1-infected people is a reasonable pathway to consider as a source for increased resting energy expenditure. Energy generated by tryptophan oxidation, especially the portion driven by viral antigens, wastes energy by uncoupling energy demands and energy oxidation, especially the portion driven by viral antigens, resting energy expenditure. Energy generated by tryptophan is a reasonable pathway to consider as a source for increased extrahepatic tryptophan oxidation in HIV-1-infected people is not an energy source unless it is in excess. Therefore, extrahepatic tryptophan oxidation in HIV-1-infected people is a reasonable pathway to consider as a source for increased resting energy expenditure. Energy generated by tryptophan oxidation, especially the portion driven by viral antigens, wastes energy by uncoupling energy demands and energy production.⁶³ In support of the notion connecting tryptophan oxidation to resting energy expenditure, de Metz and colleagues⁶⁴ showed in normal volunteers that a dose of interferon γ sufficient to raise the circulating concentrations by 15–20-fold increases the resting energy expenditure by 11%. The expected increased ATP and carbon dioxide from extrahepatic tryptophan oxidation can explain at least part of the resting energy expenditure phenomenon in HIV-1 infection. The exact contribution of this metabolism to the increased resting energy expenditure in HIV-1-positive patients remains to be quantified.⁶⁵

Changes in associated metabolites
In HIV-1-infected individuals, alterations to other molecules whose metabolism is linked to tryptophan oxidation might have additional consequences (table 2). The potential pathogenic links between decreased tryptophan and these molecules (ie, serotonin, melatonin, glutamine, l-lysine, and picolinic acid) need to be further assessed. The hydroxylative metabolism of tryptophan produces serotonin and melatonin. The concentration of serotonin in the brain depends on plasma tryptophan concentrations,⁶⁶ and several studies show clearly that serotonin in the CNS and the periphery is diminished. Although melatonin concentrations have not been studied directly, these are likely to be proportionately decreased since it is synthesised from serotonin. Decreased serotonin and melatonin could potentially result in mood and sleep disturbances. Two aminoacids whose concentrations are increased in HIV-1-infected individuals and whose metabolism is linked to tryptophan oxidation are glutamate⁶⁷ and l-lysine (figure 3).⁶⁸,⁶⁹ Lastly, picolinic acid, which is a side product of tryptophan oxidation (figure 3), can inhibit T lymphocyte proliferation,⁷⁰ and inhibit HIV-1 replication.⁷¹ Measurement of picolinic-acid concentrations in HIV have not been reported.
nicotinamide, reverses tryptophan oxidation, and this action may be central to the observed benefits. Antiretrovirals and niacin inhibit tryptophan oxidation in vivo. By contrast, any strategy that seeks to replete tryptophan in HIV-1-infected people by direct dietary supplementation of the amino acid may inadvertently fuel tryptophan oxidation, raise quinolinic-acid production, and thereby exacerbate the neurotoxic effects of tryptophan oxidation. Therapeutic strategies aimed at regulating tryptophan oxidation may prove useful for patients infected with HIV-1, particularly those who have limited dietary protein and whose routine tryptophan intake is less than that provided by the typical diet in developed countries.

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Conflicts of interest
I have no conflicts of interest to declare in relation to this review.

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