

# Chronic immune activation is the cause of aids: implication of treatment in the developing world

## Abstract

Overwhelming number of evidence suggests that chronic immune system activation and dysregulation is responsible for progression into AIDS. Levels of activation markers on CD8<sup>+</sup> and CD4<sup>+</sup> T cells and other markers of activated immune response correlate with progression to AIDS. The uncontrolled inflammatory response has been associated with damage of lymphoid organs and the gastrointestinal mucosa; thus, further affecting T cell homeostasis and causing bacterial translocation, respectively. Immune system activation persists even after viral loads have been suppressed with antiretroviral therapy, which has been associated with increased morbidity and mortality of patients. On the other hand, natural primate hosts of SIV display very little immune activation and do not progress to AIDS. Several studies have been performed with immune suppressors and modifiers on HIV patients with varying degrees of success. The immune modifier that showed the most promise of being globally accessible and affordable was applying probiotic. Probiotic treatment studies demonstrated safety and efficacy in maintaining T cell homeostasis of HIV-infected individuals. The probiotic also has the potential of being genetically manipulated to increase its effectiveness. An effective probiotic treatment for HIV infections has the potential of being grown locally in resource limited regions and by the users themselves; therefore, reducing cost of HIV treatment and prolonging the health of HIV-infected individuals.

**Keywords:** HIV; AIDS; Chronic Immune Activation; Cost-effective HIV treatment; Probiotics; Globally Accessible HIV treatment

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## Abbreviations

HIV: Human Immunodeficiency Virus, AIDS: Acquired Immuno Deficiency Syndrome, SIV: Simian Immunodeficiency Virus, ART: Anti Retroviral Therapy, WHO: World Health Organization, HAART: Highly Active Anti Retroviral Therapy, GI: Gastro Intestinal, VNP: Virologic Non-Progressors, SM: Sooty Mangabeys, AGM: African Green monkeys, LPS: Lipo Polysaccharide, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus

## Introduction

Recently we have experienced many breakthroughs in HIV treatment, such as stem cell transplants, that result in functional cure; however, none of these treatments will ever be accessible or of any benefit to places where HIV is most rampant, e.g. the developing world. Despite World Health Organization's (WHO) strides and successes in making antiretroviral therapy (ART) globally accessible there are still significant challenges to making ART accessible to the majority in low- and middle-income countries.<sup>1</sup> Additionally, long-term-usage of antiviral drugs leads to drug-resistance, which increases the demand for better and more expensive drugs, further taxing the limited funds.<sup>2,3</sup> The only effective way to increase HIV treatment availability and prolong the health of HIV-infected individuals in areas of limited resources is to make the treatment more accessible and affordable. The following review is designed to summarize the available evidence for causation of AIDS and the implication this causation has for cost-effective treatment.

## Chronic immune activation is the cause of AIDS

There is a large body of evidence that suggests that chronic immune activation and dysregulation causes the progression to AIDS. In the early stages of HIV infection high levels of pro inflammatory

cytokines are released in both plasma and lymph nodes.<sup>4</sup> This is a normal physiologic response designed to destroy pathogens and restore homeostasis; however, in the case of HIV this robust immune response has been demonstrated to be ineffective in destroying HIV and even deleterious. Multiple reports have shown a link between poor prognosis for the infected patient and high level of activation markers on CD8<sup>+</sup> and CD4<sup>+</sup> T cells, regardless of the viral load<sup>4-15</sup> The Neopterin, a molecule secreted in increased amounts by activated monocytes and macrophages, is another immune system activation marker that is used to predict the development of AIDS.<sup>16,17</sup>

The danger of this chronic immune activation to T cells has to do with the cycle that T cells go through upon activation. Activation of T cells drives them to differentiate into antigen experienced cells, which then results in a large number of these cells undergoing apoptosis. The activated CD4<sup>+</sup> T cells actually apoptose more rapidly than CD8<sup>+</sup> T cells and thus get depleted more quickly.<sup>4,18-20</sup> Additionally, the chronic immune system activation causes destruction and rapid ageing of the primary and secondary lymphoid organs and thus further interfering with normal T cell homeostasis.<sup>4,21</sup> T cell activation persists even after viraemia has been suppressed to an undetectable level in HAART-treated patients. This persistent activation in HAART-treated patients has been associated with exhaustion of lymphopoiesis and subsequently increased morbidity and mortality.<sup>22,23</sup>

Previously the prevalent thought was that direct HIV infection of CD4<sup>+</sup> T cells caused their apoptosis and led to AIDS; however, the frequency of activated CD4<sup>+</sup> T cells that undergo apoptosis greatly exceeds HIV-infected CD4<sup>+</sup> T cells.<sup>24,25</sup> Additionally, data demonstrated that the activation and dysregulation of the immune response is independent of HIV replication levels, suggesting factors other than viral replication are causing this pathological immune response and apoptosis.<sup>7</sup>

The chronic activation of the immune system not only proved to be damaging and ineffective in controlling HIV but it also creates a favorable environment for HIV replication.<sup>26-28</sup> HIV can only replicate in activated CD4<sup>+</sup> T cells and the more activated the cells are the more likely HIV is to replicate and spread; thus, propagating the vicious and damaging cycle. Activation of CD4<sup>+</sup> T cells also increases their CCR5 expression and thus making them better infection targets.<sup>29</sup>

The immune dysregulation that results during an HIV infection is further intensified by the massive loss of CD4<sup>+</sup> T cells from the gastrointestinal (GI) tract, which occurs during the first few weeks of HIV infection. This depletion of CD4<sup>+</sup> T cells at the GI tract is associated with disruption of the tight junctions and translocation of intestinal bacteria and bacterial products, which are presumed to exacerbate the hyper-immune response.<sup>21,28</sup> Some studies suggest that it is the production of pro-inflammatory chemokines and cytokines that are responsible for disrupting the GI tract epithelial barrier and causing bacterial translocation.<sup>30,31</sup>

Some compelling evidence of how damaging this hyper-activation and dysregulation comes from studies of few HIV-infected individuals termed virologic non-Progressors (VNPs).<sup>21</sup> The VNPs show signs of very low immune activation and experience stable levels of CD4<sup>+</sup> T cells for many years, while displaying similar viral loads to AIDS-Progressors.<sup>21,32,33</sup> One study demonstrated that these VNPs show a similar immune activation profile as natural hosts of SIV that do not progress to AIDS.<sup>33</sup>

### What studies with natural primate hosts reveal about the immune response and AIDS progression

More evidence implicating chronic immune system activation in progression to AIDS came through studies of SIV-infected primates. Rhesus macaques also experience progressive depletion of CD4<sup>+</sup> T cells and AIDS.<sup>34</sup> The immune system in these primates, just like in humans, is also characterized by strong T cell activation. On the other hand, SIV-infected sooty mangabeys (SM) and African Green monkeys (AGM), the natural hosts of SIV, do not progress to AIDS and have minimal T cell activation despite evident viral replication.<sup>35-40</sup> Interestingly, the SIV-infected CD4<sup>+</sup> T cells of AGMs apoptose as rapidly as human HIV-infected CD4<sup>+</sup> T cells;<sup>41</sup> thus, implying that the viral infection of these cells is not the main factor in causing the decline of CD4<sup>+</sup> T cells.

The depletion of gut mucosal CD4<sup>+</sup> T cells was first perceived to be completely responsible for progression to AIDS. Studies with SMs revealed that mucosal CD4<sup>+</sup> T cells also become depleted and spikes in LPS are seen during acute infection; however, after some time LPS levels become undetectable despite the fact that gut mucosal CD4<sup>+</sup> T cells never become restored.<sup>42</sup> The SM observation suggests that the CD4<sup>+</sup> T cells are not solely responsible in preventing bacterial translocation and the loss of gut mucosal CD4<sup>+</sup> T cells is not solely responsible for progression to AIDS. These studies with SMs imply that it is probably the hyper-active immune response with high levels of damaging cytokines that is responsible for compromising the gut mucosal barrier in HIV infected individuals.

### Modifying the immune response can prolong the health of HIV-infected individuals

The overwhelming evidence implicating the immune hyper-activation in causing AIDS implies that if we modulate the immune response to reduce the degree of inflammation and immune activation we can prolong the health of infected individuals. A few studies have been performed studying the effects of several immune suppressors, immune modifiers, cytokine inhibitors, and cytokine

boosters in HIV infected individuals with varying degrees of success and some failures.<sup>21</sup> The most cost-effective immune modifier which showing some promise in improving CD4<sup>+</sup> T cell levels and reducing inflammation is a probiotic supplement. The appeal of using Probiotics as a supplementary treatment for HIV infections lies in its low cost and potential to be synthesized in a yogurt form by the users themselves. This type of a treatment is ideal in low- and middle-income countries. A “yogurt project” in the Tanzanian community demonstrated the feasibility of locals making their own yogurt to provide to HIV-infected locals.<sup>43</sup> If we can improve upon this yogurt treatment we can potentially improve the health and quality of life for millions.

Several studies that examined Probiotics’ role in modifying the immune response in HIV patients demonstrated that Probiotics are generally safe and have a low risk of serious adverse effects;<sup>44-47</sup> however, precautions should be exercised when dealing with immuno compromised patients.<sup>48</sup> Another promising study examined the effects of Probiotics and Prebiotics supplementation in ART treated SIV-infected macaques. The supplementation with Probiotics and Prebiotics enhanced reconstitution and functionality of GI tract CD4<sup>+</sup> T cells and reduced fibrosis of colon lymphoid follicles.<sup>49</sup> The degree of success between the probiotic studies are variable and this is most likely due to discrepancies in probiotic strains, probiotic concentrations, and Prebiotics supplementations used in different studies. Some of the earlier studies with Probiotics and allergies also suggest that different probiotic strains have different effects on the immune system.<sup>50</sup> More studies need to be done in order to establish the effective concentration, strain type, and probiotic supplementation.

It is possible that by genetically modifying Probiotics we can enhance its favorable effects on the immune system. Genetically modified Probiotics that secrete IL-10, an interleukin with anti-inflammatory properties, have already been tested to be safe and effective in Crohn’s disease clinical trial.<sup>51</sup> A trial like this could be done to study the effects of genetically modified Probiotics secreting IL-7 on HIV infected patients. IL-7 is an interleukin known to increase survival of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Three clinical trials demonstrated an improvement in CD4<sup>+</sup> and CD8<sup>+</sup> T cell levels with IL-7 supplementation.<sup>21</sup>

Other possibilities in dampening and modifying the damaging immune response could be by administering particularly inflammatory HIV antigens in the context of a probiotic as an “oral tolerance” treatment. The term oral tolerance arose from the technique of using antigen ingestion for the purpose of modifying the immune response to that antigen.<sup>52</sup> The idea came from observations that immune response against ingested food antigens or bacterial flora is absent, suggesting that antigen presentation in the mucosa is modified to prevent unnecessary immune activation and inflammation. The original purpose of oral tolerance technique was to induce tolerance to auto antigens in autoimmunity disorders.<sup>52</sup> However, the term oral tolerance might be a misnomer since some cases have shown that tolerance to an antigen is not always induced, instead the immune response to that antigen is modified.<sup>53</sup> A clinical trial tested the effects of feeding HBV and HCV antigens to HBV- and HCV-infected patients demonstrated safety of this treatment, improvement in liver pathology, and the immune response to the virus.<sup>54,55</sup> If a similar response can be observed in the context of HIV infections it would be feasible to create an HIV-antigen-secreting probiotic and use it as cost-effective HIV treatment.

## Conclusion

In light of all the data pointing to immune hyper-activation and dysregulation being the culprit in transition to AIDS we need to shift

more focus on developing a treatment that will modulate the damaging immune response and prolong the health of HIV-infected individuals. The probiotic treatment shows great promise in being a globally accessible and cost-effective means to extend the health of HIV-afflicted individuals. In order to move forward we need to determine which probiotic strains, concentrations of Probiotics, and Prebiotics are most effective in modulating the damaging immune response. In addition, we should be open to the possibility of modifying the Probiotics to increase their positive effect on the immune system of an HIV-infected individual.

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## Conflicts of interest

None.

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