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The Dual Role of Neutrophils in HIV Infection

Tiffany Hensley-McBain[1,2] and **Nichole R. Klatt**[1,2,#]

[1]Department of Pharmaceutics, University of Washington, Seattle, WA

[2]Washington National Primate Research Center (WaNPRC), University of Washington, Seattle, WA

Abstract

Purpose of review—We summarize what is known about neutrophils in HIV infection, focusing on their potential roles in HIV protection, acquisition, and pathogenesis.

Recent findings—Recent studies have demonstrated that neutrophil-associated proteins and cytokines in genital tissue pre-infection associate with HIV acquisition. However, recent *in vivo* assessment of highly exposed seronegative individuals and *in vitro* studies of anti-HIV functions of neutrophils add to older literature evidence that neutrophils may be important in a protective response to HIV infection.

Summary—Neutrophils are important for containment of pathogens, but can also contribute to tissue damage due to their release of reactive oxygen species, proteases, and other potentially harmful effector molecules. Overall, there is clear evidence for both helpful and harmful roles of neutrophils in HIV acquisition and pathogenesis. Further study, particularly of tissue neutrophils, is needed to elucidate the kinetics, phenotype, and functionality of neutrophils in HIV infection to better understand this dichotomy.

Keywords

neutrophils; HIV mucosal dysfunction; HIV infection; tissue damage; mucosal immunology; HIV protection

Introduction

Neutrophils, the most abundant immune cell, are the first responders to infection and are crucial in the immune response to pathogens[1]. However they can also contribute to tissue damage through their release of reactive oxygen species and other potentially harmful effector molecules. This dichotomy could have important implications for HIV as a tissue-resident pathogen that is transmitted across mucosal tissue surfaces. Therefore, the balance of neutrophil antimicrobial function and tissue damage caused by neutrophils could greatly impact both HIV transmission and pathogenesis in several capacities as depicted in Figure 1.

[#]**Corresponding author:** Nichole R. Klatt, 3000 Western Ave., Seattle, WA 98121, Ph: 206-221-0254, klattnr@uw.edu.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Indeed, studies linking tissue neutrophils to HIV transmission as well as studies suggesting that neutrophils have a role in HIV protection have both been published[2–5]. Neutrophils, especially tissue neutrophils, have been understudied in HIV infection due to the cells' susceptibility to freezing injury and reduced viability after cryopreservation, which require that they be assessed fresh after isolation from blood or tissue[6]. For example, while it is known that peripheral neutrophils have reduced antimicrobial function in HIV infection and this is related to increased risk of secondary infection[7],[8],[9], the functionality of intestinal and reproductive tract neutrophils in HIV infection remains unexamined. Further, distinct neutrophil phenotypes have been described in various states of health and disease, yet limited work has been done to assess these phenotypes in relevant mucosal tissues in HIV infection. Here, we summarize what is known about neutrophils in HIV infection, including studies assessing peripheral neutrophil phenotype and function, the potential for tissue neutrophils to contribute to HIV pathogenesis, and the evidence that neutrophils may contribute to both HIV acquisition and the antiviral immune response to HIV.

Neutrophil Recruitment, Antimicrobial Functions, and Tissue Damage

Neutrophils are actively recruited to sites of infection by chemotactic factors as they roll along the walls of post-capillary venules searching for signs of distress[29]. Specifically, chemoattractants act on endothelial cells to upregulate selectin molecules involved in neutrophil tethering and integrins involved in neutrophil adhesion. The most potent of the host-derived chemoattractants is the chemokine interleukin-8 (IL-8), which is released by monocytes, macrophages, epithelial cells, mast cells, keratinocytes, fibroblasts, endothelial cells, and neutrophils during inflammation[30]. Importantly, circulating IL-8 levels are increased in HIV-infected persons on ART[31]. High levels of IL-8 cause increased endothelial expression of adhesion molecules and increased leukocyte transmigration, which have been proposed to contribute to the increased risk of comorbidities in treated HIV infection[32].

Once in the tissue, neutrophils employ several potent antimicrobial mechanisms to fight invading pathogens. Central to all of these mechanisms are cytotoxic granules within neutrophils that contain different types of antimicrobial molecules including 1) cationic peptides such as defensins; 2) proteases such as cathepsins, lysozyme, gelatinase, and elastase; and 3) reactive oxygen and reactive nitrogen species[33]. In degranulation, granular contents are exocytosed to kill pathogens or promote transmigration[34, 35]. Additionally, through phagocytosis, neutrophils internalize microorganisms and sequester them in a phagosome, which then merges with granules to kill the pathogen. Finally, neutrophils can release neutrophil extracellular traps (NETs) consisting of DNA to trap microbes and kill them using granule components[36]. These antimicrobial functions of neutrophils are mediated through recognition of pathogen-associated molecular patterns (PAMPs). PAMPs interact with pattern-recognition receptors (PRRs) on the neutrophil surface, including toll-like receptors (TLRs), peptidoglycan-recognition protein (PGRP), and collectins[37, 38]. Neutrophils express TLRs 1, 2 and 4–10, and TLR ligation mediates cell survival, cytokine release, superoxide generation, degranulation, and phagocytosis[39]. Additionally, neutrophils recognize complement-opsonized pathogens by surface receptors such as

CD11b/CD18 and CD11c/CD18 and antibody-opsonized pathogens through Fc receptors[39].

The antimicrobial functions of neutrophils make them a necessary component of the immune system's ability to fight pathogens. However, since their discovery they have also been viewed as inflammatory cells that cause destruction in their wake, and collateral tissue damage is often observed as a result of neutrophils' antimicrobial activities[40]. Indeed, excessive host tissue damage can be caused by unregulated control of granule proteases, and the three most commonly associated with damage are the serine proteases elastase, proteinase-3 and cathepsin G[41]. Additionally, NETs can trigger antibody-mediated autoimmune responses and organ dysfunction, and the release of toxic reactive oxygen species can cause extracellular matrix damage and tissue necrosis[42, 43].

Neutropenia, neutrophil dysfunction and secondary infections

HIV-infected individuals often experience decreased peripheral blood neutrophil counts compared to uninfected individuals, and the degree and nature of neutropenia in HIV infection has been extensively reviewed[44]. One of the largest and most recent cohort studies found that at baseline 44% of HIV-infected women had neutrophil counts less than 2000 cells/μl and during a 7.5 year follow-up period, and 79% of the HIV-infected women presented with neutrophil counts less than 2000 cells/μl on at least one occasion[45]. Importantly, this study also demonstrated that decreased neutrophil counts associate with more advanced disease progression including lower CD4+ T cell counts and higher HIV-1 RNA levels, and ART treatment protected against the development of neutropenia.

Several factors have been suggested to contribute to neutropenia in HIV infection. These have been reviewed extensively elsewhere[44], but the main contributing immunological factors will be briefly summarized here. Given the relationship between neutropenia and HIV-1 RNA levels, it has been proposed that HIV-induced cytotoxicity contributes to neutropenia. Although there are no studies demonstrating that HIV directly infects and kills mature neutrophils, HIV has been shown to destroy multipotent hematopoietic stem cells (HSC) through direct infection and Fas-dependent apoptosis, and HIV proteins suppress proliferation of granulomonocytic progenitor cells[46–49]. Additionally, HIV infection of stromal cells can disrupt the bone marrow microenvironment, thus reducing support for progenitor development and decreasing factors important for granulocyte development such as G-CSF[50],[51]. HIV also reduces the production of the neutrophil supporting cytokine GM-CSF by T cells and other mononuclear cells, and reduced GM-CSF levels correlated with fewer granulomonocytic progenitor cells in one study[52, 53]. Taken together, these studies provide evidence that HIV cytoxicity of progenitor cells and other leukocytes could contribute to reduced neutrophil production in the bone marrow. In addition to hematopoietic defects, antineutrophil antibodies produced by polyclonal B cell activation in HIV infection have been reported and associated with neutropenia[54, 55]. Finally, neutrophils from people with AIDS exhibited accelerated apoptosis compared to healthy individuals, and neutrophils in SIV-infected rhesus macaques similarly exhibited increased apoptosis, suggesting that reduced survival of peripheral neutrophils may also contribute to neutropenia[56, 57]. However, a recent study reported decreased peripheral neutrophil apoptosis and increased

neutrophil necrosis in ART-treated HIV infection, suggesting an inflammatory switch in cell death mechanism rather than overall increased neutrophil cell death may be occurring in individuals on ART[58]. In addition, there is also the possibility that increased homing to effector sites such as the mucosa or marginal pools such as those in the lung may contribute to peripheral neutropenia; however tissue neutrophils have been vastly understudied in the context of HIV infection.

Beyond neutropenia, peripheral neutrophils in HIV-infected individuals have reductions in several functions, including chemotaxis, phagocytosis, bactericidal activity, and oxidative burst abilities, which have been observed in both untreated individuals and those on ART and worsen during the course of infection[7],[8],[9],[59],[60],[61]. Importantly, the antimicrobial function of neutrophils in the tissues has not been assessed, and it is therefore unclear how neutrophil dysfunction may contribute to the lack of HIV containment in initial infection, HIV pathogenesis, or HIV reservoir. However, both neutropenia and decreased peripheral blood neutrophil functionality are linked to an increased risk of secondary infections in people with HIV, such as bacteremia, pneumonia, and aspergillosis[22–24]. Furthermore, several studies indicate that recombinant G-CSF therapy can prevent neutropenia, improve neutrophil function, and increase survival through the prevention of serious bacterial and fungal infections in people with advanced HIV disease [62–64]. Importantly, while multiple studies by the same group have revealed that neutrophil fungicidal activity is not returned to normal in patients on ART treatment despite viral suppression and CD4 reconstitution[65, 66], a comprehensive evaluation of other antimicrobial neutrophil functions following treatment has yet to be performed. This is further complicated by the fact that different ART drugs may directly impact neutrophil functionality by vastly different mechanisms, with one previous study demonstrating that dideoxynucleosides enhanced neutrophil antimicrobial functions while another study found that protease inhibitors inhibited neutrophil functions[67, 68]. These data suggest that different ART regimens likely differentially contribute to neutrophil dysfunction in treated HIV infection. Overall, the level of residual neutrophil dysfunction in treated HIV infection and the contribution of different ART regimens should be further evaluated in order to understand the extent to which neutrophil dysfunction may contribute to HIV pathogenesis in the era of ART.

The potential role of neutrophils in mucosal dysfunction and HIV pathogenesis

GI mucosal dysfunction is a defining feature of HIV infection and is characterized by structural damage to the epithelial barrier [69, 70]. This damages manifests as structural abnormalities including atrophy and blunting of enterocyte villi, crypt hyperplasia, and breaches in tight junctions that lead to increased intestinal permeability[71]. The causes and consequences of mucosal dysfunction are multifaceted and complex, and are still not completely understood[70, 72, 73]. However, putative mechanisms have been shown to contribute to reduced GI barrier integrity in HIV infection. These include: 1) death, dysfunction, and abnormal proliferation of enterocytes caused by HIV proteins[74, 75, 25, 76, 77]; 2) enterocyte apoptosis and tight junction downregulation caused by inflammatory

cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β[75, 78]; and 3) massive CD4+ T cell depletion in the GI tract in acute infection[79], including the loss of IL-17- and IL-22-producing T cells known to homeostatically maintain the epithelial barrier[80]. This mucosal dysfunction results in focal breaches in the GI epithelial barrier and allows microbial products to translocate across the GI barrier and circulate in the blood, known as microbial translocation[81, 72, 82, 83]. Ongoing microbial translocation is a central factor in persistent systemic immune activation and inflammation that occur despite ART and is associated with increased morbidities and mortality in people with treated HIV infection[84–87].

During chronic HIV infection, neutrophils infiltrate the GI tract at high levels, yet their contribution to the pathology of mucosal dysfunction in GI tissue is unknown[25]. As previously mentioned, while neutrophils are critical in protection from infections, aberrant neutrophil responses can also be harmful. Models of inflammatory bowel disease (IBD) suggest that neutrophils in the GI tract may contribute to disease, and neutrophil infiltration correlates with disease severity in patients with ulcerative colitis[88, 89]. However, some IBD models also demonstrate that depletion of neutrophils can exacerbate disease, illustrating a controversy over the role of these cells[90–92]. In favor of neutrophils contributing to mucosal damage in settings other than HIV are several studies indicating that transepithelial migration of neutrophils creates gaps between epithelial cells, alters levels of tight junction proteins, and increases epithelial permeability[93],[94],[95]. The potential role of neutrophil recruitment in inducing mucosal damage could have a critical impact on microbial translocation, systemic immune activation, and the resulting comorbidities in HIV infection.

In the SIV model of infection, increased neutrophil infiltration in the GI tract has been observed in association with increased disease progression and damage to the epithelial barrier[26], but it is unclear if this infiltration contributes to the barrier damage or is a response to contain microbial products that have translocated to the lamina propria. One study reported increased peripheral neutrophil death in acute SIV infection associated with more rapid progression to AIDS in rhesus macaques, suggesting that neutrophils may be important for controlling factors such as microbial translocation that are associated with HIV pathogenesis[19]. In rats, increased microbial translocation after neutrophil depletion has been reported, suggesting neutrophils may be critical in clearing translocated bacteria and preventing access of these bacteria and bacterial products to the periphery[90]. Importantly, the inability of neutrophils to contain microbial translocation in the context of SIV and HIV infection may be due to decreased antimicrobial function of the recruited neutrophils. Indeed, evidence that ART may improve chemotaxis but not the crucial microbe-killing functions of neutrophils further supports the hypothesis that decreased neutrophil function may contribute to microbial translocation in the setting of ART-treated, chronic HIV infection[65]. It will be critical to evaluate the antimicrobial functions of GI neutrophils during HIV infection to further assess their potential contribution to the containment of microbial translocation.

Neutrophils, inflammation, and immune dysfunction in HIV

Importantly, most of what is known about neutrophils in HIV infection pertains only to peripheral blood neutrophils and there have been no studies directly assessing the role of neutrophils in gastrointestinal immunity or dysfunction in HIV or SIV infection. Peripheral blood neutrophils of ART-treated, HIV-infected individuals have recently been described as hyperactivated, with reduced L-selectin (CD62L) and FcgRIIIb (CD16) and increased integrin (CD11b) expression, and this hyperactivation is more pronounced in individuals with inflammatory comorbidities[58]. However, it remains unclear if neutrophils directly contribute to inflammation or if microbial translocation drives both inflammation and neutrophil activation in the periphery.

Neutrophils in HIV infection may also be interfacing with the adaptive immune system and driving dysfunction. Neutrophils that act as granulocytic myeloid-derived suppressor cells (G-MDSCs) have been identified as a specific phenotype of neutrophils with the ability to suppress the adaptive immune response, particularly through suppression of T cell cytokine production and proliferation[96]. A recent study elucidated a role for suppressive neutrophils in T cell exhaustion and immune suppression in HIV infection[28]. Specifically, the authors found that blood neutrophils in HIV-1 infected individuals have increased PD-L1 expression and suppress T cell function via a mechanism involving reactive oxygen species and PD-L1 interaction with the T cell surface molecule PD-1. Another recent study demonstrated that low density granulocytes, including G-MDSCs with increased arginase release, inversely correlated with CD4+ T cell count and positively correlated with plasma HIV RNA[27]. Importantly, the activation and functionality of gastrointestinal neutrophils in HIV infection remains unknown, and the expression of functional markers such and PD-L1 has yet to be assessed on GI neutrophils in HIV infection, making this an important area for future study to better elucidate a role for these cells in GI immune dysfunction.

Neutrophils and HIV protection

Two studies have demonstrated associations between increased risk of HIV acquisition and fewer peripheral blood neutrophils, implicating neutrophils in a protective role against HIV *in vivo*[4, 5]. In one such study of South African high-risk female sex workers, HIV-uninfected women with a genetic basis for ethnic neutropenia and circulating neutrophil counts <2500 cells/μl had a ~3-fold increased risk of acquiring HIV infection compared to those with higher neutrophil counts[4]. Additionally, in another cohort of South African women, higher neutrophil counts in the mother and infant were each associated with lower risk of perinatal HIV infection, with each 1000 cells/μl increase in the infant's neutrophil count at birth associated with an 11% reduction in the risk of perinatal HIV acquisition[5].

A pivotal role for neutrophils in viral immunity has been more recently established and neutrophils could contribute to an anti-HIV response in several ways. First, α-defensins, also known as human neutrophil peptides (HNP), are produced mainly by neutrophils and have potent antiviral properties[12]. HNP1, HNP2, and HNP3 inhibit HIV infection *in vitro* by directly inactivating the virus or by blocking viral replication by altering target cell signaling pathways[10–13]. Importantly, highly exposed seronegative (HESN) men in Uganda had

elevated α-defensins in the foreskin, suggesting they may contribute to a protective mucosal environment[97]. The release of myeloperoxidase (MPO) and reactive oxygen species by neutrophils to form hypochlorous acid has also been demonstrated to be viricidal to HIV-1 *in vitro*[14]. The anti-HIV properties of defensins and MPO can be potentially concentrated and directed by capturing the virus in extracellular traps, as was recently demonstrated by neutrophils *in vitro*[17]. Neutrophils participate in antibody-dependent cell-mediated cytotoxic killing of HIV-infected cells, but less effectively than monocytes and NK cells[15, 16]. Lastly, neutrophils can perform antibody-dependent cellular phagocytosis of infected cells and immune complexes, a function that constitutes part of the polyfunctional HIV-specific antibody response described in elite controllers[18]. In a recent *in vitro* study comparing phagocytic ability of tissue resident cells, neutrophils exhibited more robust phagocytosis of gp120-coated fluorescent beads compared to macrophages from colon and similar phagocytic ability compared to cervical macrophages, further highlighting a role for neutrophil phagocytosis in the anti-HIV immune response[98].

Neutrophils and HIV acquisition

Despite studies indicating a potential role for neutrophils in the anti-HIV response and protection against HIV, several other studies have linked neutrophils or neutrophil-associated factors to increased HIV acquisition. In one study, neutrophils isolated from the blood of HESN individuals expressed lower levels of PRR and cytokine mRNAs *ex vivo* and demonstrated reduced cytokine production in response to TLR and HIV-1 stimulation when compared to neutrophils from infected individuals[2]. These data suggest reduced neutrophil responses may be associated with protection from HIV infection. Although the HESN individuals also expressed lower levels of some of the PRR and cytokines examined when compared to uninfected controls, it remains unclear if neutrophils in HIV-infected individuals are more responsive overall compared to uninfected individuals and how that may confound comparisons between HESN and infected individuals. Additionally, a study of Kenyan female sex workers demonstrated that high levels of HNPs 1–3 and the cathelicidin LL-37 in cervicovaginal secretions were associated with subsequent HIV acquisition despite their contribution to the ability of the genital secretions to neutralize HIV *in vitro*[20]. Additionally, the potent neutrophil chemokine IL-8 was among the pro-inflammatory cytokines increased in cervicovaginal lavages (CVL) from South African women who acquired HIV infection when compared to women who remained uninfected in the microbicide trial CAPRISA 004[21].

As mentioned previously, the unregulated release of proteases and other factors into the extracellular space can paradoxically damage host tissues by degrading structural proteins of mucosal surfaces[99, 34]. As proteases help neutrophil migration and penetration through tissue via tissue remodeling and extracellular matrix degradation, proteases therefore facilitate barrier disruption. Indeed, further study of CVL from the CAPRISA 004 trial associated increased neutrophil proteases with increased inflammatory cytokines, an altered cytoskeleton, and increased endocervical CD4+ T cells[100]. The authors also demonstrated that neutrophil proteases correlated positively with IL-17 expression. This is not surprising given that neutrophils and Th17 cells participate in reciprocal recruitment through the production of chemokines, and the Th17/neutrophil axis has been well studied in several

bacterial and viral infections[101–103]. Importantly, this axis could represent a role for neutrophils in increasing the number of target cells for HIV acquisition and replication as Th17 cells have been demonstrated to be preferentially infected in the female genital tract[104, 105]. Finally, this link between neutrophils and HIV target cells has also been observed in men. Specifically, one study associated increased odds of seroconversion with penile coronal sulcus IL-8 levels, and the authors further demonstrated that high IL-8 levels associated with increased neutrophils and increased HIV target cell density, including Th17 and Th1 cells, in the foreskin[3]. Thus, overall, there is clear evidence for both helpful and harmful roles of neutrophils in the context of HIV infection. It is possible that this dichotomy is due to a lack of studies assessing tissue neutrophil functionality *in vivo* or *ex vivo* in high risk groups, as the protective evidence is based mainly on peripheral blood neutrophil frequencies or the *in vitro* anti-HIV function of neutrophils while the acquisition evidence is based mainly on neutrophil supporting cytokines or neutrophil factors measured in tissues *ex vivo*. Studies assessing the anti-HIV functions of tissue neutrophils and/or their contribution to tissue damage in relation to HIV acquisition would be useful in understanding the conflicting results of the studies performed thus far and better elucidate their potential role in protection and acquisition.

Conclusion

There are many unanswered questions regarding neutrophil kinetics and functionality that could greatly impact the role of neutrophils in HIV pathogenesis and acquisition. HIV infection results in neutrophil dysfunction in chronic infection, yet it is unclear when neutrophil dysfunction occurs and to what extent neutrophil dysfunction alters the ability of neutrophils to participate in an antiviral response or contribute to HIV mucosal dysfunction and pathogenesis. With regards to tissue neutrophils in the genital tract, further studies are necessary to fully elucidate the dichotomy of ongoing neutrophil accumulation pre-infection and the association with HIV risk and a transient neutrophil recruitment to the genital mucosa that may contribute to a protective antiviral response. However, reducing neutrophil accumulation and unresolved neutrophil-driven inflammation in high-risk individuals should be investigated as a potential HIV prevention strategy. Additionally, the capacity in which neutrophils contribute to the antiviral response to HIV and SIV remains unclear. While studies have linked low peripheral neutrophil frequencies to increased HIV acquisition risk and SIV disease progression, no studies have fully assessed the necessity of neutrophils in a protective response, particularly at mucosal sites. Finally, while the propensity for neutrophils to damage mucosal tissue is apparent, the extent to which they contribute to mucosal dysfunction in HIV remains unknown. The field would benefit greatly from *in vivo* studies in HIV-infected individuals, as well as in the nonhuman primate or humanized mouse models, that target neutrophil frequency or functionality to better elucidate the role of neutrophils in protection and/or acquisition and their contribution to mucosal damage in HIV pathogenesis.

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Conflict of Interest

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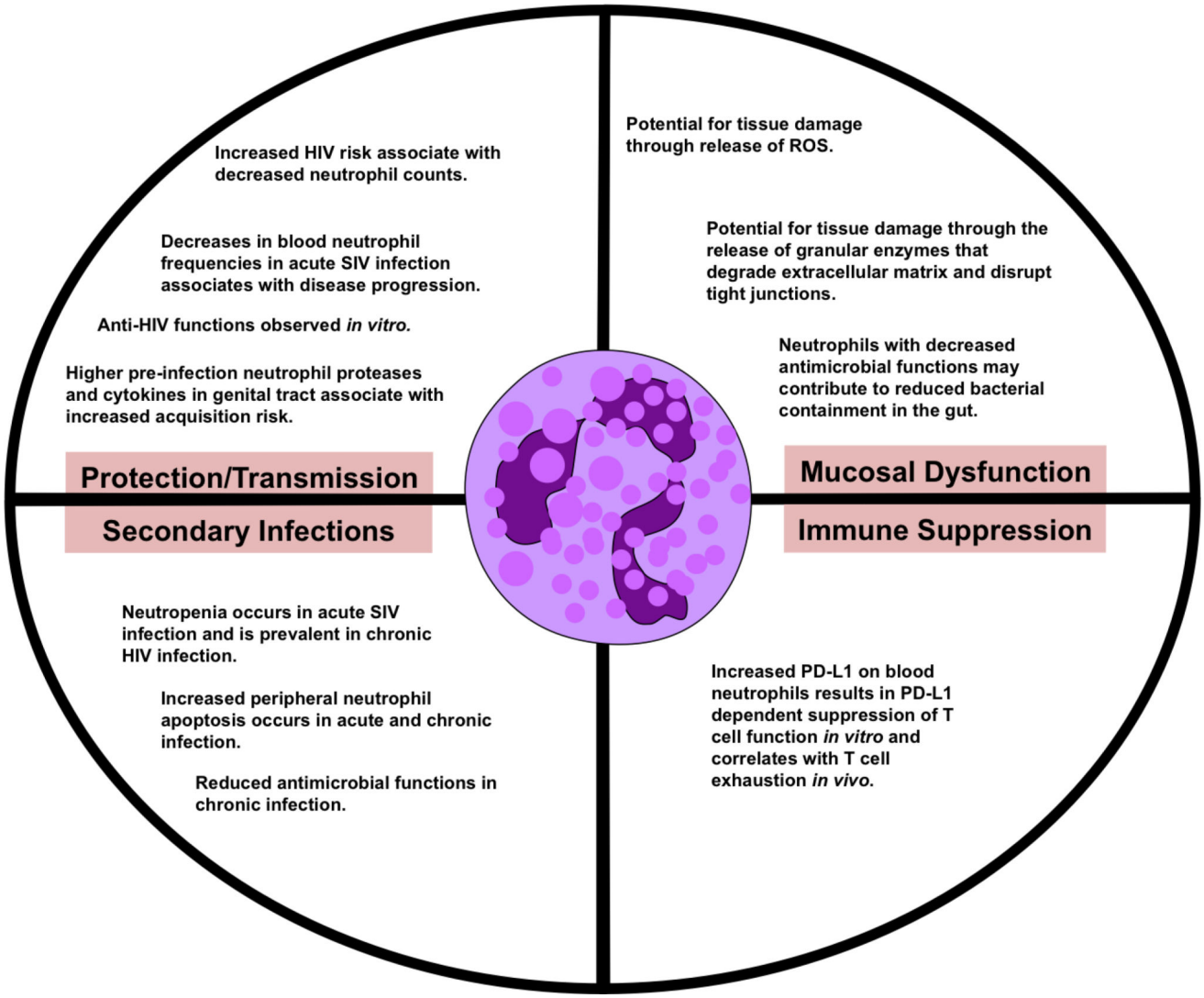

Figure 1. Neutrophils in HIV/SIV infection

Neutrophils could have a diverse impact on HIV infection depending on their location, kinetics, and functionality. Most of what is known about neutrophils in acute infection is based on non-human primate SIV infection studies. **Protection/transmission:** *In vitro* studies demonstrate anti-HIV functions of neutrophils[10–13], [14], [15, 16], [17], [18], and reports correlate reduced peripheral blood neutrophil frequencies with increased HIV acquisition risk and SIV disease progression *in vivo*[4, 5, 19]. There have been no studies assessing mucosal neutrophil frequencies and acquisition risk in SIV or HIV infection. Contrarily, higher levels of neutrophil factors in the genital tract pre-infection associate with HIV acquisition risk *in vivo*[3, 20, 21]. **Secondary infections:** Neutropenia and neutrophil dysfunction are associated with increased risk of secondary infections in HIV-infected individuals[22–24]. **Mucosal dysfunction**: A direct link between neutrophils and mucosal dysfunction has yet to be assessed but it is proposed that neutrophils could contribute to tissue damage and that neutrophil dysfunction may allow microbial translocation[25, 26]. **Immune suppression**: Neutrophils can act as granulocytic myeloid derived suppressor cells

that suppress T cell function and increased suppressor activity of peripheral neutrophils has been observed in HIV infection[27]. PD-L1 expression on neutrophils correlates with PD-1 expression on CD4+ T cells, which is a marker of exhaustion and marks cells enriched for integrated HIV DNA during suppressive ART[28].