HIV Infection and Gut Mucosal Immune Function: Updates on Pathogenesis with Implications for Management and Intervention

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Abstract HIV is primarily a sexually transmitted infection. However, given that the gastrointestinal tract (GIT) houses most of the body’s lymphocytes, including activated memory CD4+ T cells that are preferential targets for HIV, recent research has focused on the role of the GIT in transmission and pathogenesis. In health, the GIT maintains a balance between immune tolerance and rapid responsiveness. A complex network of innate and adaptive responses maintains this balance, which is severely perturbed in HIV infection. Recent studies have focused on mechanisms of GIT CD4+ T-cell depletion and epithelial disruption in HIV infection, the role of inflammation in accelerating viral dissemination, the kinetics of the adaptive response following transmission, and the extent of T-cell reconstitution following antiretroviral therapy. This review summarizes the results of recent investigations that may have important implications for the development of vaccines, microbicides, and therapeutic interventions for HIV and other mucosal pathogens.

Keywords HIV · AIDS · Gut · Mucosa · Transmission · Virus · CTL

Introduction

The gastrointestinal tract (GIT) is arguably the most important target organ for HIV. Although the high incidence of HIV-associated gastrointestinal disorders, diarrhea, and wasting was recognized early in the epidemic, it was initially unclear, even among gastroenterologists, why the GIT would serve as a major target for infection. Subsequent research revealed that the distinction between the mucosal and peripheral immune systems, the presence of physiologic baseline inflammation with immune cell activation, and increased co-receptor expression on intestinal T cells make the GIT a prime target for HIV infection regardless of infection route. Nevertheless, more than 25 years into the epidemic, the initial mucosal target cell(s) for HIV infection remain undefined, and the mechanisms driving the spiraling inflammation that enhances HIV replication and dissemination are only now being elucidated, as are the mechanisms promoting immune control in certain rare individuals. Given the novel and often poorly understood features of the GIT and the capacity of HIV to escape immune pressures while inflicting significant damage on the host, further studies are needed to elucidate the host-pathogen relationship in acute, chronic, antiretroviral-treated, and end-stage disease. This review highlights recent research findings on HIV and the GIT from the published literature.

The GIT and Mucosal Immunology

The GIT, which is about 26 ft long, houses most (40%–65% or more) of the body’s total immune cells [1]. These cells are organized into two types of structures consistent with their role in the mucosal immune system (Fig. 1). Inductive sites (eg, Peyer’s patches in the small intestine
and lymphoid follicles in the colon) are organized aggregates analogous to peripheral lymph nodes. In inductive sites, antigen-presenting cells (APC) provide processed antigen to naïve lymphocytes within distinct T- and B-cell zones. Mucosal effector sites consist of intraepithelial and lamina propria lymphocytes disseminated throughout most of the GIT. Intraepithelial lymphocytes in humans are primarily CD8+ T cells with a minority (<10%) of γδ T cells. Throughout the large and small intestine, the single-cell columnar epithelium is underlain by a basement membrane, beneath which lies the lamina propria, heavily populated in health with CD4+ T cells and some plasma cells. Macrophages and dendritic cells are present in both inductive and effector sites.

Less often referred to as “immune cells,” gut epithelial cells provide a critical barrier function but also express major histocompatibility complex (MHC) class II and Toll-like receptors and secrete several cytokines. Microfolded cells, or M cells, are modified epithelial cells that take up and transfer antigen and some pathogens to underlying inductive sites. Epithelial and stromal cells, as well as APC and lymphocytes, secrete cytokines, chemokines, and other factors that can be finely tuned to promote tolerance, inflammation, or specific immunity. Notably, intestinal biopsies from healthy individuals produce moderate levels of cytokines, sometimes higher than those seen in HIV-infected patients on antiretroviral therapy (ART) [2]. This low-grade inflammatory state likely reflects ongoing contact with intestinal flora, and appears to be tightly regulated to maintain mucosal integrity and clinical health.

Important in any discussion of HIV and GIT mucosal immune cells is the concept that mucosal T cells, in health, are baseline “activated” by nearly any definition and are mainly (>98%) of the memory (CD45RO+) phenotype. Furthermore,
mucosal CD4+ T cells are predominantly CCR5+/CXCR4+, constitutively expressing the essential co-receptors for HIV infection; fewer than 20% of these CD4+ T cells exist in blood [3–5]. The activation status, memory phenotype, and co-receptor profile of GIT CD4+ T cells render them extremely susceptible to infection with CCR5- and CXCR4-tropic strains of HIV, as well as highly productive in terms of viral protein synthesized per cell [4]. These characteristics underscore the vulnerability of GIT T cells in healthy individuals to HIV infection, and also identify mechanisms supporting the massive lateral dissemination and ongoing infection in HIV-positive individuals.

As a background to the following discussion, it may be helpful to view “chronic” HIV infection as a series of ongoing, acute infections occurring daily, to which the immune system responds, adapts, and provides defensive immune cells and reparative efforts. Integral in this response is that repetitive, local cytokine/chemokine secretion may be both harmful and helpful. While recruiting HIV-specific CD8+ T cells to the site of infection, cytokines/chemokines also lead to increased recruitment of HIV-susceptible CD4+ T cells. Proinflammatory cytokines may also contribute to weakening the epithelial barrier, leading to translocation of microbial products into peripheral circulation and ultimately to generalized immune activation [6, 7].

Clinical Presentations and “HIV Enteropathy”

Clinical presentations of acute HIV infection often include diarrhea, dehydration, chills, and loss of appetite, but just as frequently, GIT clinical manifestations are limited although mucosal immune destruction is underway. During end-stage AIDS, GIT presentations and diagnoses are multiple, complicated, and poorly responsive to treatment [8*, 9]. The clinical presentation in the well-controlled and/or reconstituted HIV-infected patient presents a more difficult diagnostic and treatment plan, and identifies diverse mechanisms altered by HIV infection. This presentation is usually related to multiple dysfunctions/dysregulations occurring concurrently, each requiring independent identification and treatment that presents challenges for the physician and the patient. The factors contributing to gastrointestinal discomfort or frank dysfunction include opportunistic infection (usually with <100 CD4+ T cells/mL), medication reaction, fat malabsorption, bacterial overgrowth, functional bowel disease (usually diarrhea predominant), bile salt excess, and direct HIV-driven mucosal inflammation, which is a form of inflammatory bowel disease (IBD) [3, 10].

It is this last diagnosis that many refer to as “HIV enteropathy.” However, given the presumptive underlying role that HIV may play in all the clinical components mentioned, this term is becoming a catch-all akin to “HIV-related diarrhea.” The term “enteropathy” may be more appropriate because it does not exclude nondiarrheal cases. Some cases may be effectively managed by controlling HIV with improved ART. Others require more complex approaches. Precisely because of the multifactorial pathways, despite a presumed common etiology (HIV), a single therapeutic intervention, usually effective in most HIV-seronegative presentations, will not suffice. As our ability to detect novel gut pathogens and our understanding of mucosal immune and inflammatory processes advances, treatment for such cases will likely improve, but effective diagnosis and treatment will continue to require a multidisciplinary approach [8*, 10].

Acute HIV Infection and the Gut: Which Cells Are Infected?

As early as the mid-1990s, clinicians studying HIV-related enteropathy reported abnormalities in intestinal leukocyte subsets, including a depletion of CD4+ T cells in upper and lower GIT [11]. Experimental infection of macaques with simian immunodeficiency virus (SIV), which is closely related to HIV, revealed depletion of intestinal CD4+ T cells within days of infection [12]. Remarkably, the kinetics of gut CD4+ T-cell depletion were similar regardless of whether the infection route was mucosal (rectal or vaginal) or intravenous [12]. This finding likely reflects the extreme permissiveness of lamina propria CD4+ T cells to HIV/SIV infection. The extent to which intestinal macrophages and dendritic cells are infected remains controversial. Intestinal macrophages reportedly lack expression of HIV coreceptors and are relatively nonpermissive for infection [13]. Productively infected dendritic cells were detected in intestinal tissues of SIV-infected macaques in at least one study [14]. In humans, intestinal dendritic cells express DC-SIGN (dendritic cell-specific ICAM-3 grabbing nonintegrin) and can transfer HIV to T cells in vitro; however, whether they are infected in vivo is less clear [15].

How Does Rectal Transmission Occur?

Although it is established that gut CD4+ T cells serve as a major target of HIV infection, the actual sequence of events leading to HIV acquisition via rectal exposure remains unclear (Fig. 1). HIV may directly access the lamina propria through breaches or tears in the epithelium, thought to be common during receptive anal intercourse. The simple columnar epithelium lining the rectal mucosa is significantly more fragile than the stratified squamous epithelium found in the ectocervix and vagina. Second, the mucosa contains dendritic cells that may bind HIV and transfer
intact virions to susceptible CD4+ T cells [15]. A third potential source of entry is via intestinal epithelial cells [16] and/or M cells [17]. Although gut epithelial cell lines may be experimentally infected in vitro, there are no confirmed reports of productively infected gut epithelial cells in vivo. However, they may take up virus via transcytosis, or by binding via an alternative receptor such as galactosyl ceramide, and then transfer the virus to CD4+ T cells. Intestinal epithelial cells express CCR5 and can transfer intact, infectious virus particles to subjacent CD4+ T cells in vitro; this process was proposed as a potential explanation for the observation that strains of HIV using CCR5 predominate during acute infection [16].

How Are Gut CD4+ T Cells Depleted?

Once infection is established, lamina propria CD4+ T cells may be killed by a combination of mechanisms, including direct infection and bystander apoptosis. Studying the SIV model, Mattapallil et al. [18] quantified the number of infected memory CD4+ T cells in blood, lymph nodes and jejunum during acute infection. Their findings suggested that 30% to 60% of gut memory CD4+ T cells were infected by 10 days postintravenous infection, corresponding to the peak of acute viremia. These results were based on quantitative polymerase chain reaction to detect viral DNA. In contrast, a report by Li et al. [19] suggested that only 7% of gut CD4+ T cells were productively infected at the peak of acute infection, but a far greater percentage was induced to undergo bystander apoptosis, perhaps after contact with viral proteins. Direct killing of infected cells by natural killer cells or cytotoxic T cells (CTL) are additional mechanisms that may contribute to CD4+ T-cell loss. However, adaptive responses apparently develop “too little and too late” in mucosal tissues to effectively control the spread of virus to draining lymph nodes, and ultimately to other tissues throughout the body [20, 21].

Epithelial Dysfunction and Immune Activation

Normal intestinal barrier function is maintained by molecular complexes that form between adjacent epithelial cells: tight junctions, adherens junctions, and desmosomes [7]. In addition, mucosal integrity requires that a variety of cells interact in a complex network mediated by cell surface interactions, soluble cytokines, growth factors, and hormones. Gene expression analysis shows that acute HIV infection is accompanied by increased production of proinflammatory cytokines and altered expression of genes related to mucosal repair and regeneration [22]. These changes, coupled with the loss of certain T-cell subsets, may lead to impaired barrier function. Altered intestinal permeability is associated with leakage of bacterial products, notably lipopolysaccharide (LPS), into plasma. Brenchley et al. [6] reported that plasma LPS levels and bacterial ribosomal DNA were elevated in patients with chronic HIV infection as compared with healthy controls. Furthermore, LPS levels correlated with measures of innate and adaptive immune activation, and were reduced in patients undergoing ART. Subsequent studies revealed that experimental administration of LPS to SIV-infected African green monkeys leads to increased viral load and intestinal CD4+ T-cell depletion [23]. Taken together, these findings suggest a direct link between increased epithelial permeability and the generalized immune activation observed in HIV infection. However, as many studies in the IBD literature have shown, this observation is not specific to HIV [24].

Depletion of Intestinal Th17 Cells

An important subset of CD4+ T cells, designated Th17 because of their production of interleukin (IL)-17, appears to be preferentially infected and depleted during acute HIV/SIV infection. Th17 cells secrete both IL-17 and IL-22, which in turn induce the production of other cytokines, β-defensins, and other antimicrobial peptides important for host defense. These cells are considered particularly important for mucosal defense against opportunistic pathogens, including fungi such as Candida albicans, and for maintaining epithelial integrity. Relative to controls, SIV-infected macaques coinfected with Salmonella typhimurium showed increased dissemination of Salmonella, which was associated with depletion of mucosal Th17 cells [25•]. This finding suggested that IL-17 deficiency contributes to defective intestinal barrier function and host protection.

Acute Damage to Mucosal Inductive Sites

It has been known for many years that HIV infection leads to destruction of lymph node architecture, including disruption of the follicular dendritic cell network and involution of germinal centers. However, the effects of acute infection on Peyer’s patches were not studied in detail until recently. Levesque et al. [26] investigated B cells in blood and terminal ileum from patients during acute/early infection. They found a loss of germinal center architecture in Peyer’s patches, with an abundance of apoptotic T and B cells. Acute HIV infection also induced polyclonal B-cell activation in both blood and the GIT, stimulating production of antibodies specific for influenza and autoantigens.
Gut Immune Responses: Too Little and Too Late?

Why are host defenses unable to clear HIV near the site of transmission before the infection becomes systemic? Strong evidence exists that CD8+ T cells contribute significantly to the control of virus replication [27]. The appearance of CTL in blood following acute infection coincides with the post-acute decline in plasma viremia. Second, depletion of blood CD8+ T cells from SIV-infected macaques using anti-CD8 monoclonal antibodies leads to a resurgence of plasma viremia. Third, CTL can exert immunologic pressure on specific viral sequences, leading to the outgrowth of escape mutants. Fourth, the rare individuals who naturally control HIV without ART frequently have strong, polyfunctional, HIV-specific CD8+ T-cell responses [28•]. Why, then, do CTL not clear foci of acute infection in mucosal tissues? The answer may be related to at least three issues: timing, location, and the involvement of an inflammatory cascade.

The amount of time required for an adaptive, cell-mediated response to be induced in mucosal inductive sites and travel to effector sites (ie, lamina propria) may depend on the efficiency of antigen uptake and presentation in a particular tissue. Following intravenous infection with SIVmac, CTL specific for SIV antigens appeared at a similar rate in blood and intestinal mucosa, reaching high levels in both by 2 weeks after infection [29]. However, following intravaginal inoculation, CTL specific for SIV were not detected in the female reproductive tract until nearly 3 weeks after infection [20]. Detailed studies of intrarectal infection have not yet been reported, but it appears likely that gut CD4+ T-cell depletion begins before the arrival on the scene of antigen-specific CTL.

The Potential Importance of In Vivo Effector-to-Target Ratio

The importance of CTL location and effector-to-target (E:T) cell ratios was underscored in a recent report by Li et al. [30••], who quantified SIV-infected CD4+ T cells and CTL in mucosal tissues following intravaginal infection of macaques; detailed studies of this type have not yet been reported for intrarectal infection. High in vivo ratios (ie, >100:1), in which numerous CTL were located in close proximity to infected cells in the female reproductive tract, were associated with significant reductions in viral load during early SIV infection. Low E:T ratios were not. The investigators reported similar findings in murine lymphocytic choriomeningitis virus (LCMV) infection [30••]. Although perhaps not surprising, these are among the first studies to report on virus-specific CTL in actual tissue, rather than the more conveniently sampled, often-reported blood samples. Without direct analysis of tissues, it is impossible to know the in vivo spatial relationship between effector and target cells. These findings, and this new analytical approach, provide a hopeful message that an HIV vaccine approach capable of inducing CD8+ T cells that traffic to potential sites of transmission might be effective.

Inflammation Accelerates Viral Dissemination

Recent studies suggest that inflammation facilitates viral dissemination beyond the site of initial infection. Using an intravaginal inoculation model in macaques, Li et al. [31••] demonstrated that early production of macrophage inflammatory protein-3α (CCL20) is followed by an influx of plasmacytoid dendritic cells near the site of infection. These cells, in turn, secrete chemokines capable of attracting more CCR5+CD4+ T cells to the cervicovaginal mucosa, where they will rapidly become infected. Notably, this process could be blocked by the topical administration of an antimicrobial, anti-inflammatory compound, glycerol monolaurate [31••].

These studies were performed in a model for intravaginal exposure, and they highlight the rationale driving the field of topical microbicide development. These promising new agents work by either blocking HIV’s access to target cells, limiting target-cell vulnerability (specifically by modulating their activation state and/or coreceptor availability), or by interfering with HIV’s ability to replicate once inside target cells. Parallel studies are under way using rectal mucosa [32]. As an important component of a combination approach toward reducing HIV transmission, microbicides may provide short-term protection that will complement mucosal vaccination strategies.

Mucosal Neutralizing Antibodies

By definition, neutralizing antibodies (NAb) work best when their concentration near the site of exposure is sufficiently high to block virus entry into host cells. At the mucosal surface, NAb might function by blocking the interaction of HIV with its receptor/coreceptor, or by blocking nonspecific virus uptake and transcytosis by epithelial cells or M cells. Antibodies can also mediate antibody-dependent cell-mediated cytotoxicity through interaction with natural killer cells.

An enormous challenge in the field of HIV vaccine development is the question of how to induce high concentrations of NAb at the sites of potential transmission. Interestingly, in two important studies, systemically administered combinations of neutralizing IgG antibodies protected macaques from pathogenic mucosal challenge (one
oral, one intravaginal) [33]. These findings imply that IgG from peripheral circulation can be exuded at mucosal surfaces and protect these surfaces from infection.

Several studies have reported the detection of HIV-specific IgA in plasma or mucosal secretions from individuals who are highly exposed to HIV yet persistently seronegative (HEPS) [34]. By definition, such individuals lack HIV-specific antibodies in plasma; therefore, this finding suggests that a compartmentalized antibody response was elicited in mucosal tissues upon repeated exposure to antigen, and that class switching also occurred locally. Some studies of HEPS have failed to detect such antibodies, and the topic remains controversial [35•]. Nevertheless, Tudor et al. [36•] recently described the construction of a Fab expression library from cervical B cells isolated from HEPS women. IgA antibodies specific for the membrane-proximal region of HIV gp41 were obtained from this library. These antibodies neutralized infectivity of X4 and R5 HIV strains in vitro, and blocked transcytosis.

Even if these findings are confirmed, the problem of how to induce local production of HIV-specific IgA and/or IgG antibodies through vaccination of HIV-negative subjects remains daunting. Recently, a small phase 1 study investigated mucosal responses to a live vaccinia recombinant expressing HIV-1IIIB env/gag/pol after deltoid or inguinal vaccination of HIV-seronegative volunteers. Disappointingly, no HIV- or vaccinia-specific antibodies were detected in rectal secretions [37].

**Cell-Mediated Immunity During Chronic Infection: Are Gut CD8+ T-cell Responses Inadequate?**

Given the extensive depletion of CD4+ T cells that begins during the acute phase, and the persistence of virus in the GIT throughout chronic infection, the question arises whether HIV-specific T-cell responses in the gut are absent, delayed, and/or dysfunctional [20]. One study of chronic HIV infection found few HIV-specific CD8+ T cells in terminal ileum, one site of severe CD4+ T-cell depletion, in contrast to abundant CTL in bronchoalveolar lavage, a luminal fluid in which CD4+ T cells are relatively well preserved [38]. This report suggested a positive correlation between mucosal CD8+ T-cell responses and the maintenance of CD4+ T cells, but also underscored the difficulty in drawing general conclusions regarding mucosal immunity from samples taken at a single site. The relatively low HIV-specific CD8+ T-cell responses measured in terminal ileum suggested that CTL may be inadequately recruited to some portions of the GIT (ie, inductive sites), or functionally impaired [38].

CD8+ T cells in rectal mucosa express low levels of the cytotoxic effector protein perforin despite an abundance of granzymes A and B, suggesting that they, too, may be functionally impaired [39]. This observation was not limited to HIV/SIV-specific CD8+ T cells, but also applied to rectal CD8+ T cells from healthy controls. Although it is possible that immune activation leads to continuous degranulation of mucosal CTL, it also seems likely that perforin expression in the gut is subject to tight regulation in health, limiting inadvertent damage to the mucosal epithelium [21]. Again, this balance may be disrupted in HIV infection.

CD8+ T cells in GIT of infected macaques express high levels of PD-1, a marker associated with immune exhaustion [40]. Furthermore, one recent study proposed the hypothesis that damage to the gut epithelium releases the adherens junction protein E-cadherin into the lamina propria and into circulation [41]. E-cadherin serves as a ligand for the inhibitory receptor KLRG-1 on CD8+ T cells. Accordingly, epithelial damage in HIV/SIV infection might indirectly trigger inhibition of CD8+ T-cell responses. Taken together, these findings suggest several potential mechanisms by which mucosal CD8+ T-cell responses may be impaired in the setting of HIV infection.

Although mucosal CD8+ T-cell responses are unable to fully clear infection, in some individuals these responses are surprisingly strong, broad and polyfunctional. In one study, rectal CD8+ T-cell responses to HIV peptide pools were mapped using the enzyme-linked immunosorbent spot (ELISPOT) technique in samples from untreated, chronically infected subjects [42]. Rectal CD8+ T cells were directed toward a broad range of peptide pools, and mirrored responses in blood. Critchfield et al. [43, 44•] studied rectal CD8+ T-cell responses to HIV peptides in chronically infected patients. Generally, strong and polyfunctional HIV Gag-specific CD8+ T-cell responses in rectal mucosa were associated with low viral load. In a follow-up study, Ferre et al. [28•] found that rare individuals with spontaneous control of HIV infection (HIV controllers) had significant preservation of CD4+ T cells in rectal mucosa compared with patients with high viral load. Surprisingly, HIV controllers also had unusually strong and polyfunctional rectal Gag-specific CD8+ T-cell responses, often associated with protective MHC class I alleles (ie, HLA-B57, B27). These strong responses may represent the high in vivo E:T ratio necessary to effectively control HIV replication in tissues.

**ART and the Gut: Is Partial or Full CD4+ T-Cell Restoration Feasible?**

Several studies of patients on long-term ART have evaluated potential correlates of gut CD4+ T-cell restoration. Estes et al. [45] found that CD4+ T-cell depletion in
terminal ileum, including Peyer’s patches, is accompanied by extensive fibrotic damage and collagen deposition. This fibrosis may disrupt the ability of gut-associated lymphoid tissue (GALT) to support normal cell-cell interactions, trafficking, and survival. When ART was begun during early infection, damage was limited, but not completely avoided [45]. HIV proviral DNA reportedly persists in CD4+ T cells from terminal ileum after up to 9.9 years of ART [46]. Furthermore, modeling based on 3 years of longitudinal data from fully suppressed subjects suggested that proviral DNA in mucosal T cells does not significantly decay during ART [47].

Sheth et al. [48] found significant CD4+ T-cell reconstitution in sigmoid colon of patients on long-term ART. However, samples of terminal ileum were not evaluated, so it remains unclear whether the differences between this and the previously cited studies are related to sampling site or other factors. What is generally agreed upon is that regardless of the level of immune reconstitution with therapy, CD4+ mucosal T cells rarely are reestablished to preinfection levels [7, 9].

Other studies of patients on long-term suppressive ART reported partial restoration of epithelial barrier function [49], central memory T cells, Th17 cells, and polyfunctional T-cell responses [50]. A common theme in most studies is that early treatment is associated with less severe tissue damage and more significant repair and T-cell reconstitution. Nevertheless, HIV DNA stably persists in the GIT despite long-term suppressive ART regimens, supporting the concept of ongoing, low-level replication, which presents a challenge for eradication efforts [46, 47].

Conclusions

Although gastrointestinal disorders and CD4+ T-cell depletion were first recognized many years ago as characteristic of acute HIV infection, the implications of these observations were not fully recognized until recently, when the field of HIV research “rediscovered” the GIT. The refocusing of HIV research to emphasize the critical role of tissue-based investigations in understanding HIV pathogenesis, from acute infection to advanced disease, has been an essential and welcome paradigm shift. As we develop a better understanding of the delicate balance between tolerance and immune responsiveness in the gastrointestinal mucosa, we are hopeful that meaningful progress will become possible on several fronts, including the development of novel mucosal vaccine/adjuvant combinations, effective microbicides, improved antiretroviral therapies, and strategies to eradicate latently infected cells.

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