The gastrointestinal tract and HIV pathogenesis

Abstract
Gastrointestinal dysfunction has been recognised as a major manifestation of the human immunodeficiency virus (HIV) infection usually presenting as diarrhoea which may or may not be due to the presence of an opportunistic infection of the GIT. Contrary to earlier assumptions, there is now substantial evidence to demonstrate that there are significant changes in the gut in the acute phase of HIV infection; the most significant of these being the substantial loss of the CD4+ T-cells in the GIT. Delays in the initiation of HAART (that is, once the CD4+ T-cell count drops below 200 cells/μL), is associated with a greater severity of HIV-associated GIT enteropathy, and poor clinical outcome.

Introduction
Gastrointestinal dysfunction has been recognised as a major manifestation of the human immunodeficiency virus (HIV) infection since the earliest recognition of the syndrome, the acquired immune-deficiency syndrome (AIDS). It was originally thought that these disease manifestations were the sequelae of the immune destruction which characterises AIDS, rather than it being central to the pathogenesis of AIDS. In the past decade, it has been observed that the mucosal immune system and the intestinal immune system are pivotal in the pathogenesis of AIDS, with the most critical events, namely transmission, viral amplification, and CD4+ T-cell destruction occurring in the gastrointestinal tract (GIT). Furthermore, the breakdown of the mucosal barrier with consequent microbial translocation, are considered to be major drivers of AIDS progression. In this regard, the GIT mucosal tissue is not only a primary site of viral transmission, but also a major site of viral replication, CD4+ T-cell destruction, regardless of the route of transmission.

HIV enteropathy
GIT enteropathy in persons living with HIV (PLWH) can occur from the acute phase of infection, through to advanced disease. It is characterised by diarrhoea, increased GIT inflammation, increased intestinal permeability (up to fivefold higher than in healthy individuals), malabsorption of bile acids, and vitamin B12. Histologically, the GIT enteropathy in HIV involves inflammatory infiltrates of lymphocytes and damage to the GIT epithelial layer (which includes villous atrophy, crypt hyperplasia and villous blunting). These pathological changes may occur in the absence of any detectable bacterial, viral or fungal enteropathogens, which are often associated with enteropathy. HIV enteropathy was reported as early as 1984.

Although the mechanisms that cause the abnormalities in HIV enteropathy, are poorly understood, it has been suggested that HIV has a direct “virotoxic” effect on the enterocyte. It has been observed that the HIV accessory protein Tat has an inhibitory effect on glucose uptake in the enterocyte. HIV gp120 has been found to result in increased concentrations of calcium in the enterocyte, which is associated with tubulin depolymerisation, and a decrease in epithelial cells’ ability to maintain ionic balances. It has also been postulated that HIV may result in abnormal differentiation of the enterocyte, as it has been found to be in the proximity of abnormally enlarged enterocytes. Local activation of the GIT immune system is also thought to play a role in HIV enteropathy. In HIV there are high levels of proinflammatory mediators such as beta chemokines interleukin-6 (IL-6), interleukin-10 (IL10) and interferon (IFN-γ) found in the lamina propria of the colon in PLWH. The degree of inflammation has been found to correlate with the level of viral replication. Although systemic immune activation is a hallmark of HIV, the aetiology of the latter remains elusive. It has also been postulated that local bacterial translocation across the damaged tight epithelial barrier, results in microbial products that stimulate the immune system locally, presumably through receptors such as Toll-like receptors. A crucial consequence of induction of local inflammation through any means, is through HIV’s preferential infection of activated CD4+ T-cells, which in turn augments the HIV replication.
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Lineage cells, and on a chemokine receptor, during acute infection. Depletion of the CD4+ T-cells involves the entire GIT. The largest number of mucosal memory CD4+ T-cells are found in the GIT, and significant depletion of these cells occurs in the first 17 days post HIV infection. In a recently postulated model (based on GIT biopsies), it is thought that the bulk of CD4+ T-cell depletion occurs in the first two to three weeks of acute infection.

More recently, it has been observed that the CD4+ T-cells which bear the CCR5 HIV co-receptor are the primary targets of HIV. The CD4+ T-cells with CCR5 receptors constitute the majority of the CD4+ T-cells. It is estimated that nearly eighty percent of the T-cell population is found in the GIT.

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PLWH with a CD4 count of less than 200 cells/ul, have been found to have a twofold increase in diarrhoea. The latter affirms the view that diarrhoea is an AIDS defining condition. A decrease in CD4+ T-cells (less than 200 cells/ul) has been observed to be associated with intestinal parasitic infections, such as Cryptosporidium, Isospora and Cyclospora, and with a higher incidence of diarrhoea.

Th17 cell loss and impairment of mucosal integrity

HIV mediated loss of Th17 cells from the gut-associated lymphoid tissue (GALT) has been observed to impair mucosal integrity, and innate defence mechanisms against gut microbes. Th17 cells are important for intestinal homeostasis. Th17 cells are involved in epithelial regeneration, and stimulate the production of defensins and mucin, as well as induce the expression of claudins, which are components of epithelial tight junctions. The Th17 cytokine, interleukin-22 (IL-22) increases the production of the lipopolysaccharide binding protein (LBP) in the liver. Considering, the massive CD4+ T-cell depletion in the lamina propria after HIV infection, it is probable that Th17 cells are also depleted by HIV. Since Th17 cells have multiple roles in controlling epithelial integrity and microbial invasion, the depletion of Th17 is likely to affect the integrity of the GIT. To date, Salmonella has been directly shown to translocate across the GIT barrier, when the degree of lactose malabsorption was found to be significantly greater in PLWH with advanced disease, versus those in the earlier stages of disease. The degree of lactose malabsorption was also related to whether PLWH were symptomatic and had intestinal manifestations, than asymptomatic PLWH and non-HIV infected controls. It is presumed that apart from the presence of the HIV, other factors (probably both structural and immune) determine the enterokinetic alterations responsible for lactase deficiency and lactose malabsorption.

Clinical presentation of enteroopathy

A high percentage of PLWH worldwide have been reported to initially present with, or develop diarrhoea, irrespective of whether they are on HAART or not. In the United States, 50% of PLWH have presented with diarrhoea. However, in developing countries a prevalence of as many as 80% of PLWH have presented with diarrhoea. The presentation of diarrhoea may or may not be in the presence of an opportunistic infection of the GIT. The opportunistic infections that affect the GIT in PLWH include parasitic infections (for example: Cryptosporidia, Isospora and Cyclospora), viral [in particular Cytomegalovirus (CMV)], and bacterial [for example: Mycobacterium tuberculosis (TB), Salmonella, Shigella, Campylobacter jejuni and Mycobacterium avium complex (MAC)]. Prompt treatment of CMV is very important, as it is associated with a poor prognosis in PLWH and a high rate of recurrence. A person with GIT MAC usually has disseminated disease, a very low CD4+ T-cell count, and limited survival time. Since the introduction of HAART, the incidence and prevalence of MAC has decreased. TB of the GIT may affect immune-compromised and immune-competent individuals. It is estimated that GIT TB accounts for 1 to 3% of TB cases worldwide. It is commonly found in the region of the ileocaecal valve, but can occur at any region throughout the GIT.

Clinical presentation of HIV-associated diarrhoea varies among PLWH depending on the principal section of the GIT that is involved. Small bowel diarrhoea tends to result in large bulky postprandial stools almost immediately after eating, and the individual may experience postprandial paraumbilical abdominal pain. However, if the affected individual fasts, the diarrhoea significantly decreases. Individuals with small bowel diarrhoea usually experience weight loss. Whilst individuals with large intestine diarrhoea (termed “colitic diarrhoea”) usually present with frequent, small-volume stools, and the stools may have visible blood and mucus. These individuals will usually experience lower-quadrant abdominal pain, and the sensation of rectal urgency. However, in many instances, it may be difficult to differentiate between small- and large bowel diarrhoea.

Opportunistic infections are not limited to the small- and large bowel, and may occur in the upper GIT, including oesophageal pathology (for example: candida oesphagitis, CMV, and herpes simplex virus), and gastric and duodenal pathology (for example: CMV, Helicobacter pylori and cryptosporidium). These infections may lead to dysphagia and gastric ulceration. It has been reported that lactose malabsorption is significantly higher (70%) in PLWH, than HIV-uninfected controls (34%). Furthermore, the degree of lactose malabsorption was found to be significantly greater in PLWH with advanced disease, versus those in the earlier stages of disease. The degree of lactose malabsorption was also related to whether PLWH were symptomatic and had intestinal manifestations, than asymptomatic PLWH and non-HIV infected controls. It is presumed that apart from the presence of the HIV, other factors (probably both structural and immune) determine the enterokinetic alterations responsible for lactase deficiency and lactose malabsorption.
and hence poor nutritional intake but also recurrent dehydrating vomiting.4

Most of the GIT opportunistic infections described will result in further aggravation of HIV-associated enteropathy, due to structural damage and/or immune sensitisation; hence making it difficult to differentiate whether the severity of GIT related symptoms is due to HIV disease progression or the severity of other opportunistic infections.

In a recently published study, Densupsoontorn et al (2009)9 reported that HIV-infected children with a higher severity of malnutrition and more advanced stages of HIV clinical symptoms, had accelerated whole gastrointestinal transit time. The authors recommended early nutritional intervention for children with severe malnutrition and advanced HIV disease with specialised lactose-free feeds of low osmolality to aid in delaying gastric GIT transit time and to allow for greater nutrient absorption.

The role of gut in HIV disease progression

Immune activation in chronic HIV infection includes polyclonal B cell activation, increased turnover of T-cells, a high frequency of “activated” phenotype T-cells as well as increased levels of cytokines and other proinflammatory mediators. This activation results in the restoration of CD4+ T-cells and immunocompetence but the negative effects include lymph node fibrosis, thymic dysfunction, clonal exhaustion, drainage of memory T-cell pools and generation of more targets for HIV replication.3

It has been speculated that due to the massive depletion of memory T-cells in the gut, as well as structural defects of the GIT lining, microbial translocation from the gut is probably involved in driving immune activation. It is thought that the gut-derived microbes or microbial products translocate to the systemic circulation in the absence of overt bacteremia.3

Quantification of microbial translocation

Microbial translocation can be quantified by measuring plasma levels of lipopolysaccharide (LPS), the endotoxin produced by bacteria that have translocated across the GIT lining. PLWH with acute HIV infection were found to have LPS levels similar to those of non-HIV infected individuals. However, in PLWH with chronic HIV infection, the LPS levels were significantly higher. In an earlier study, non-infected HIV individuals were injected with LPS produced of non-HIV infected individuals.2

HAART and the gastrointestinal tract

Currently, ART has, in most cases, been found to reduce plasma viral loads to undetectable levels resulting in subsequent increases in peripheral blood CD4+ T-cells. Early studies of HIV-associated enteropathy after the initiation of ART documented significant decreases in GIT symptoms, namely, abdominal bloating, cramping and loose stools. However, a decrease in viral replication and CD4+ T-cell reconstitution does not occur at a similar rate at all anatomic sites, especially in the GIT. Recent studies have shown that in the small bowel CD4+ T-cell reconstitution was poor, and in PLWH with acute HIV infection who had been on highly active antiviral therapy (HAART) had a much greater reconstitution (twofold) of CD4+ T-cells when compared with individuals with chronic HIV infection (the latter individuals rarely ever reconstituted GIT CD4+ T-cells to normal levels). Importantly, it was also observed that although many PLWH treated with HAART reconstituted peripheral CD4+ T-cells, no HIV-infected individual ever reconstituted GIT CD4+ T-cells to levels observed in non-infected individuals.2

GIT CD4+ T-cells have been observed to still produce HIV virus, even years after the initiation of HAART. Although the GIT is well vascularised and ART drugs should be bioavailable, high levels of multidrug-resistant proteins, also named “toxin pumps” (such as P-glycoprotein), are expressed on the apical surface of columnar epithelial cells of both the small and large intestine. It is speculated that these multidrug-resistant proteins, have specificity for protease inhibitors and nucleoside analogs and may reduce the local concentration of ART drugs to infected cells in the GIT, thus allowing the virus to slowly replicate and limit reconstitution of CD4+ T-cells.5

Ongoing local inflammation in the GIT maybe a second reason for the failure of PLWH on HAART to reconstitute CD4+ T-cells. Local immune activation has been shown to be associated with fibrosis of the lymphoid architecture in peripheral lymph nodes, which in turn influences the degree of peripheral blood CD4+ T-cell
reconstitution following the initiation of HAART. Recent findings also suggest that the fibrotic deposition of collagen also occurs in the GIT Peyer’s patches, even during the acute phase of HIV infection. The degree of architectural damage of the Peyer’s patches predicts GIT CD4+ T-cell depletion after HAART. Although HAART reduces GIT immune activation, it is thought that the ability of the remaining (but damaged) lymphoid to support significant CD4+ T-cell reconstitution is permanently damaged. As many as 30% of PLWH on HAART, fail to reconstitute CD4+ T-cells, despite HIV-viremia control, and are described as immunologically-nonresponders (INRs). INRs have an increased risk of HIV/AIDS progression.11

Plasma citrulline: A biomarker of enterocyte mass in PLWH?

Plasma or serum citrulline assays have recently emerged as being the best tool in assessing enterocyte mass, irrespective of the aetiology of the intestinal mucosal disease. Citrulline is the metabolic product of glutamine, and its related amino acids, and arginine, and is specifically synthesised by small bowel enterocytes. Citrulline has been validated for quantitative enterocyte assessment in villous atrophy disease. Citrulline plasma levels are not influenced by nutritional status, level of hypoalbuminaemia, or inflammatory status. The only limitation in interpreting plasma levels is the presence of significant renal failure (creatinine clearance of < 30 ml/min) because citrulline is metabolised into arginine in the proximal convoluted tubules in the kidneys. A recent study12 reported that plasma citrulline assays were a reliable indicator of severe chronic infectious enteropathy in PLWH, and hence a reliable predictor of the need for parenteral nutrition (PN) for such cases. A low citrulline level of < 10 umol/L is considered an indication for PN, whereas for an individual with a citrulline level of > 10 umol/L, enteral route nutritional support is recommended. Citrulline is easy to measure through ion-exchange or reverse-phase liquid chromatography, which could be performed in better equipped hospital laboratories.12

The role of HIV vaccines in enhancing GIT mucosal cell immunity

There is some promising evidence which suggests that direct surgical introduction of a vaccine, (replication-competent recombinant adenovirus (rAd) vectors, specifically rAd5), rather than oral gavage, resulted in 100-fold higher transgene expression, and which stimulated potent CD8+ T-cell responses in the intestinal and systemic compartments. These responses could be further enhanced through intramuscular rAd5 injections.12 The activation status of CD8+ T-cells is considered to be one of the best predictors of HIV disease progression.5

Conclusion

In conclusion, the better understanding of the pathophysiology of HIV enteropathy has contributed to the better management of diarrhoea in PLWH. Further research is likely to yield other therapeutic approaches which will further facilitate the management of diarrhoea and contribute to further improvements in the quality of life of PLWH.

References: