HIV and the Gastrointestinal Tract

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The gastrointestinal (GI) tract plays a key role in both the clinical manifestations and pathogenesis of HIV infection. As a mucosal surface, the GI tract serves as an important barrier between pathogens in the external environment and the body's sterile internal environment [1]. The tight epithelial junctions, as well as the local immune system of the GI tract, protect against pathogenic organisms. However, in the face of HIV infection, normal defenses are disrupted, leading to a wide range of clinical and pathogenic consequences.

GI symptoms are reported by 50–70% of HIV-infected persons, with even higher percentages among those residing in the developing world [2,3]. Diarrhea, the most common GI complaint, can occur during both acute HIV infection and advanced disease. Within days of HIV infection, an intense infiltration of virus-laden lymphocytes is present within the bowel wall and may manifest as diarrhea during seroconverting illness [4,5]. Over time, chronic changes ensue with diminution of the protective mucosal barrier. Opportunistic infections may occur as the CD4 T cell count falls below 100–200 cells/mm^3 including a myriad of viral, bacterial, fungal, and parasitic pathogens (Figure 1) [2,5,6].

Beyond the risk for opportunistic pathogens, HIV itself alters the structure and function of the GI tract. In 1984, Kotler et al. noted histological changes in the GI tracts of HIV patients in the absence of other defined infectious or malignant etiologies and termed the condition "HIV enteropathy" [7]. The diagnosis of HIV enteropathy is one of exclusion, requiring a thorough work-up of all other potential causes (Figure 1).

The pathogenesis of HIV enteropathy is the result of both direct and indirect effects of the virus - gp120 negatively affects tubulin depolymerization, and induction of local cytokines (e.g., interleukin (IL)-6, IL-10, tumor necrosis factor) causes altered epithelial ionic balances and enterocyte apoptosis [1,8,9]. These changes result in both structural and immunological abnormalities. On histological sampling of the small intestine and colon, villous atrophy, crypt hyperplasia, epithelial hypoproliferation, and CD4+ (CD4+CD45RA−CD69+CCR5+) depletion within the lamina propria are seen [5,10,11]. The associated inflammation, increased permeability, and malabsorption (of bile acids and vitamin B12) all contribute to the diarrhea that can occur with HIV enteropathy.

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With the advent of highly active antiretroviral therapy (HAART), opportunistic etiologies, along with HIV enteropathy, dramatically decreased [12,13]. HAART not only improves the systemic immune system, but also the local cellular immunity of the GI tract. Hence, HAART became the cornerstone for both the prevention and treatment of opportunistic GI infections and HIV enteropathy [2]. The case described by Ebama et al highlights this important point [14]; despite therapeutic trials with antimicrobials and nutritional support, diarrhea persisted until HAART was begun. Studies have demonstrated that HIV enteropathy frequently improves within a week of HAART initiation [12].

Why then are we still discussing diarrhea among HIV-infected persons in the HAART era? Although HAART has clearly reduced the impact of some GI conditions, diarrhea remains an important cause of morbidity and mortality among HIV-infected persons. Reasons for this are severalfold. First, in locations where HAART is not universally available, diarrhea due to opportunistic infections and HIV enteropathy remains a leading cause of death. Further, in the U.S. since 45% of patients are diagnosed late in the disease course [15], wasting and diarrhea, unfortunately, remain common diagnoses – this point is highlighted by the case reported by Ebama et al [14]. Moreover, in areas where the diagnosis and management of HIV occurs early, other etiologies of diarrhea have appeared including diarrhea associated with the antiretroviral medications themselves (e.g., protease inhibitors), which can impact both the patients' quality of life as well as medication adherence [6]. Finally, even with HAART, HIV patients may have persistent HIV-related pathogenesis occurring within the GI tract.

Over the past several years, the importance of the GI system as a preferential site of HIV replication and continued CD4 T cell destruction has been realized [16]. Studies have shown that within days of infection there is massive depletion of CD4 T cells within the gut-associated lymphoid tissue (GALT) [17]. Since the reconstitution of CD4 T cells is slower and less complete in the GI tract compared to the peripheral blood [18], the GI tract remains an important site of HIV pathogenesis, even during the HAART era [19].

The reasons for the incomplete immune reconstitution in the GI tract may be attributed to 1) persistent viral replication (due to low local concentrations of antiretrovirals or overexpression of multidrug transporters); 2) differential loss of certain CD4 T cell subtypes (e.g., producing IL-17); and 3) immune activation and inflammation in the gut microenvironment [18,20,21]. Of particular importance is that disturbances in mucosal integrity may result in microbial translocation. Several groups have detected elevated levels of lipopolysachharides (LPS) and other bacterial products within the systemic circulation (despite the receipt of HAART), which may contribute to immune activation leading to local and systemic CD4 T cell activation and cell death, and ultimately HIV progression [4,22]. Of note, the degree of immune activation has been shown to predict HIV progression better than the plasma HIV viral load [23].

Although HAART has dramatically changed the course of HIV, it has yet to fully restore normal life expectancy among those infected [24]. Part of the reason may be residual involvement of the GI tract; ongoing immune activation and inflammation may play a role in the development of conditions contributing to excess mortality in this population. Further studies of HIV-induced pathogenic processes within the gut are needed [25].

In summary, the GI tract was recognized early in the epidemic as an important site of HIV-related complications including opportunistic infections and HIV enteropathy. Remarkable progress in understanding the role of the GI system during both early and late phases of HIV infection has been made over the past 30 years. However, the GI system remains at the center of HIV pathogenesis, and novel therapeutic strategies addressing ongoing local HIV

replication and immune activation are needed. Such steps may be the missing link for HIV-infected persons to achieve complete virologic control, and to one day achieve the normal life expectancy that all desire.

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Figure 1.
Work-up of Diarrhea in the HIV Patient*