

Diarrhea and HIV in the US in the post-HAART era

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January 16, 2008

INTRODUCTION

Human Immunodeficiency virus (HIV) has been called one of the most destructive pandemics in the history of the world. In the U.S. the incidence of HIV was over 42,000¹ and contributed to over 13,000 deaths in 2004.² In Maryland, HIV was responsible for 480 deaths in 2006.³ These statistics are relatively low when compared to 2007 estimates from the United Nations Programme on HIV/AIDS who calculated the global prevalence of HIV at 33.2 million with an incidence of 2.5 million and attributable mortality of 2.1 million.⁴

HIV causes depletion of the immune system leading to Acquired Immune Deficiency Syndrome (AIDS). With the immune system functioning poorly, AIDS leads to often-fatal opportunistic infections. HIV affects every system of the body from the immune system to the nervous system to the gastrointestinal (GI) tract. GI symptoms are seen in up to 50% of North American or European patients with AIDS and up to 90% of those in developing countries.⁵

A common manifestation of enteric involvement of HIV is diarrhea. Diarrhea is often difficult to define and can include watery or liquid bowel movements that are more frequent than usual for the patient. Acute diarrhea lasts a few days while chronic diarrhea lasts longer. The Centers for Disease Control defines chronic diarrhea as two or more loose or watery stools a day for at least thirty days.⁶ HIV can cause diarrhea by causing changes in intestinal transit and absorption and alterations of the immune system leading to opportunistic infections. Further, diarrhea can be caused by medication side effects. Acute or chronic diarrhea can cause malnutrition, weight loss, electrolyte imbalance, and ultimately death.

Treatment for HIV changed dramatically in the mid-1990's with the concept of highly active anti-retroviral therapy (HAART). The use of combination antiretrovirals increased from 2% to 82% between 1995 and 1997.⁷ This was associated with a decline in mortality from 29.4 per 100 person-years to 8.8 per 100 person-years.⁷ Even in the era of HAART, diarrhea is more common in those that are HIV-positive, than those who are seronegative, even when accounting for age, sex, race, level of education, and income.⁸ This paper will review the causes of diarrhea in those with HIV in the post-HAART era with an emphasis on the United States.

GASTROINTESTINAL TRACT

The general cellular structure of the GI tract includes a mucosa, submucosa, muscularis propria, and adventitia. The mucosa consists of an overlying layer of squamous cells with some specialized cells, including Langerhans' cells that process antigenic signals and communicate with lymphoid tissue.⁹ The mucosa also contains an underlying layer, the lamina propria, which consists of connective tissue, vascular structures, and leukocytes. The lymphatic vessels are located in the submucosa along with lymph follicles, nerve fibers, and blood vessels. Below that is the muscular layer. This structure is seen throughout the members of the GI tract.

The mucosa of the small intestine is distinctive as it forms finger-like villi with absorptive and secretive cells overlying a central core of lamina propria. Between each villus is a crypt that extends down to the muscularis mucosa. The colonic mucosa is flat with tubular crypts that extend down to the muscularis mucosa. See Figure 1 and 2.

The gastrointestinal tract has localized organized lymphoid tissue within the mucosa and submucosa. This tissue is the Gut-Associated Lymphoid Tissue (GALT), which is separate and distinct from the systemic immune system. This lymph tissue is the largest immunologic organ in the body.¹⁰ Lymphoid nodule aggregates, known as Peyer's patches,

and solitary lymphoid nodules are scattered throughout the small intestine, colon, and rectum and contain naive B- and T-cells, and antigen presenting cells. Overlying the lymph tissue is follicle-associated epithelium with absorptive cells and M (membranous) cells, which are specialized to the small and large intestine. M cells transcytose macromolecules from the intestinal lumen to the underlying lymph cells. See Figure 3. The M cells in the rectal mucosa are potential sites for entry of HIV.

Antigens presented to the immature B- and T-cells induce immune responses. The activated lymphocytes leave the Peyer's patches, travel through the peripheral blood and return to the lamina propria of the tissue where they were initially activated. The lamina propria and surface mucosa of the intestinal epithelium contains scattered mature CD8 cells, CD4 helper cells, and B cells.

HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus with a spherical shell and cone-shaped core. See Figure 4. The core contains the capsid membrane p24 along with the nucleocapsid protein p7/p9, the genomic RNA and the pathogenic viral enzymes (protease, reverse transcriptase and integrase). Overlying the core, the envelope contains the glycoproteins gp120 and gp41. The glycoproteins help bind HIV to target cells, including CD4 helper cells, macrophages, and dendritic cells. Gp120 binds to CD4 receptor on the cell which leads to a conformational change in the gp120 molecule exposing a site for the immune cell co-receptors CCR5 and CXCR4. The binding of these receptors leads to a change in gp41 causing insertion of gp41 into the cell membrane and fusion of the virus and the cell. Chemokines naturally use the CCR5 and CXCR4 receptors and high levels of chemokines can interfere with HIV fusion. Further defects in CCR5 and CXCR4 can decrease the development of AIDS in those exposed to HIV.

There are multiple strains of HIV. One line of HIV infect monocytes, macrophages and new peripheral T-cells, these are the M-tropic strains. M-tropic cells use the CCR5, the beta-chemokine receptor. T-tropic strains infect only T-cells via the CXCR4 alpha-chemokine receptor. CCR5 is expressed on monocytes and T-cells, and these cells can be infected by the M-tropic strain. Primary T-cells express CCR5 and CXCR4. There is a difference in the third variable loop (V3) of gp120 of the M- and T- tropic strains. Much of the HIV transmitted is M-tropic but over the course of individual infection, T-tropic viruses accumulate. T-tropic viruses are believed to be more virulent and adept at depleting T-cells leading to the rapid final phase of disease progression.

HIV leads to depletion of infected immune cells by cell lysis upon viral release, and apoptosis of uninfected cells, which may be mediated by extracellular HIV-1 gp120.¹¹

HIV infection and the mucosa of the GI tract

HIV can enter intestinal mucosa through intraluminal mechanisms including transcytosis via intestinal M cells, through or between epithelial cells. Transport requires a primary receptor and a chemokine receptor (CXCR4 or CCR5). In the intestinal epithelium itself, the primary receptor is a luminal glycolipid, galactosylceramide (GalCer), which binds with high affinity to gp120.¹² Epithelial cells, including M cells, express GalCer and CCR5.¹³ Lamina propria lymphocytes express CD4 as the primary receptor and both CCR5 and CXCR4, while lamina propria macrophages express CD4 but neither of the chemokine co-receptors.^{11 14} This suggests that the lamina propria lymphocytes can be infected by either HIV-1 strain, while the macrophages remain immune.

In primary HIV-1 infection, intestinal CD4 T-cells are more profoundly depleted than peripheral T-cells.¹⁵ HIV replicates more effectively in activated T-cells, thus the intestinal mucosal T-cells are more susceptible to HIV infection and support higher levels of viral replication on a per-cell basis as compared to peripheral blood T-cells.¹⁰ In addition, naïve cells in the Peyer's patches are spared from destruction as they are immature and have decreased level of cellular activation and chemokine receptor expression.¹⁰ In study of CD4 T-cells in GALT, Guadalupe et al. showed that restoration of CD4 T cells in GALT is near-complete if HAART is begun early in infection, but delayed and incomplete if HAART is begun later.¹⁶

HIV infected cells within the Peyer's patch may act as dormant reservoirs. In a recent evaluation of HIV-1 DNA and RNA in the GALT of subjects with maximal suppression (less than 50 copies of HIV RNA per milliliter of blood) of HIV replication by HAART, HIV-1 RNA and DNA were found in biopsied specimens.¹⁷ This suggests that GALT can act as a reservoir for HIV even when the patient appears adequately treated with HAART based on blood values of CD4 and viral load.

ETIOLOGY OF DIARRHEA

Since the introduction of HAART the incidence of diarrhea in HIV has decreased.⁸^{18 19} Despite this advance, diarrhea is still more prevalent in HIV. In a case-control study at the outpatient primary care and Infectious Disease clinics at Bellevue Hospital and the Veterans Affairs Hospital in New York City in 2002 to 2003, HIV-positive and seronegative controls were asked to complete a survey regarding frequency and consistency of bowel movements, as well as health related quality of life (HRQOL). Of the 163 HIV-positive subjects, the median CD4 count was 370 with 40 having a CD4 <200 and 150 taking HAART. Diarrhea was more common in HIV, even when accounting for age, sex, race, level of education, and income (OR 6.65; 95% CI, 3.36-13.17).⁸ Diarrhea was significantly more likely to occur in those with HIV by all measures of diarrhea as shown in Figure 5, drawn from the Siddiqui article. Lower CD4 counts only trended towards increased incidence of diarrhea ($p=0.08$), while protease inhibitor use and older age were associated with significantly increased incidence of diarrhea ($p=0.004$, and $p=0.002$, respectively). See Table 1. Further those with diarrhea scored lower on HRQOL questionnaires indicating worse HRQOL, see Tables 2 and 3. This study is limited by its reliance on self-reported data, the use of only urban population, and the prevalence of male participants. Further this study did not ascertain the cause of diarrhea.

A similar incidence of diarrhea was found in a larger cohort study of HIV-positive persons enrolled in the Nutrition for Healthy Living (HFHL) study.²⁰ The participants in this study were recruited at inpatient, outpatient and community settings to partake in a longitudinal nutritional study. For this survey, current diarrhea was defined three or more loose or watery stools per day in the past month and the CDC definition of chronic diarrhea as two or more loose or watery stools a day for at least 30 days. (CDC) Of the 671 HIV positive participants, the mean CD4 was 356 with 45% on HAART, see Table 4. Nearly 40% experienced diarrhea, which was more likely in men ($p=0.022$). Diarrhea was more common in those with AIDS (CD4 <200 or an AIDS defining illness), but was not more common in those with just CD4<200. The limitations of this study include the reliance of self reported data.

Few studies have attempted to evaluate the cause of diarrhea in the post-HAART HIV population. Call et al performed a retrospective review of AIDS (CD4 <200) patients at a Birmingham, Alabama primary care clinic between 1995 and 1997, a period before and

after the introduction of HAART.¹⁸ They found the occurrence of chronic diarrhea ranged 8-10.5% and remained stable over the study. Chronic diarrhea was defined as greater than 3 stools per day for greater than two weeks. The incidence of opportunistic infections decreased from 53% to 13% (p=0.003), and the incidence of medication associated diarrhea increased from 0% to 45% (p=0.001), see Figure 6 and Table 5. One advantage of this study is the cause of diarrhea was evaluated using stools studies and endoscopy. Limitations include the retrospective nature, relying on accurate charting and the inability to standardize work up, and the localized study group.

OPPORTUNISTIC INFECTIONS

An important cause of the morbidity and mortality of GI tract disorders in HIV is due to opportunistic infections. These infections occur with the immune system is compromised, usually with CD4 counts <200, but can occur with those on HAART and normal CD4.^{18 19}

Fungal

Histoplasma capsulatum

Histoplasmosis can occur as an opportunistic infection in endemic areas, including the Ohio, Mississippi, and Missouri River valleys of the United States. Caused by *H. capsulatum*, 10% of those with disseminated infection have GI symptoms including diarrhea, weight loss, obstruction, bleeding, and abdominal pain.²¹ Treatment is with amphotericin B or itraconazole.²¹

Microsporidia

The two most frequently pathogenic species of microsporidia: *Enterocytozoon bienersi* and *E. intestinalis*. There is continuous debate whether these organisms are fungi or protozoa.^{22 23} Microsporidiosis is difficult to diagnose due to their small size, but with a thorough evaluation, including trichrome, Warthin-Starry, and Giemsa stains and electron microscopy of small bowel biopsies, microsporidia can be found. Prior to the frequent use of HAART, Microsporidia was present in up to 20% of diarrhea in those with CD4<50 and up to 60% of chronic diarrhea.²⁴ These organisms cause a watery diarrhea without fever and anorexia by causing crypt hyperplastic villous atrophy with blunted villous tips.²⁵ Treatment is albendazole, but this is only effective against *E. intestinalis*, or immune reconstitution.

Protozoan

Parasitic infections can cause significant diarrhea. The diarrhea is often chronic and voluminous, and can lead to need for electrolyte and fluid replacement. Many of the studies of protozoan diarrhea focus on developing countries, thus making accurate assessments of diarrhea in the U.S. difficult. In a review of chronic diarrhea by Oldfield, parasites were more likely to be the cause of HIV-related diarrhea in those with prolonged symptoms, weight loss, not on HAART, and CD4 <100.²³ Resolution of diarrhea occurred in 85% of those affected by raising the CD4 count with HAART.

Cryptosporidium sp.

Cryptosporidiosis is a common infection in those with AIDS, occurring in 10-20% of those in the U.S in the pre-HAART era. HAART has reduced the incidence of Cryptosporidiosis by raising CD4 count.²³ The most common species affecting humans are *Cryptosporidium hominis* and *C. parvum*, which are found in contaminated water. These

parasites infect the small and/or large intestine causing a chronic, voluminous watery diarrhea, severe abdominal cramps, anorexia, malaise and fever. Those with CD4<150 often remain symptomatic until counts rise but may be colonized indefinitely.^{26 27} Coexisting small bowel cytomegalovirus is seen in 38% of those with extensive small bowel cryptosporidiosis.²⁵ There is no adequate treatment, but first line is nitazoxanide.²⁸

Isoospora

Isoospora belli is similar to *Cryptosporidium spp.* as it infects the small bowel and causes watery diarrhea, malaise, and abdominal cramping. It occurs in those with CD4 <100 and is less frequent in the United States than in developing countries.²⁹ Treatment is with Bactrim and suppression continues indefinitely.

Cycloospora and *Giardia*

Cycloospora cayetanensis is a food and waterborne parasite often associated with raspberries, blackberries, and blueberries. *Giardia* is found often in the small bowel of those with AIDS. It is seen in those with and without diarrhea, and treatment does not improve symptoms.

Bacterial

Patients with HIV are more likely to have bacterial diarrhea than those who are seronegative. The incidence of bacterial diarrhea (7.2 per 1000 person-years) is 100-fold greater in those with HIV than among the general US population, and those with more advanced immunosuppression are at a greater risk for developing bacterial diarrhea.³⁰ Common bacterial causes of bacterial diarrhea include *Clostridium difficile*, *Shigella*, *Campylobacter*, *Salmonella*, and mycobacteria. See Figure 7. Despite the increased risk of bacterial diarrhea in those with HIV, the incidence of all causes of bacterial diarrhea has decreased over the past few decades, likely due to the use of HAART.³⁰

Clostridium

Clostridium difficile is the most common cause of bacterial diarrhea in HIV. In a large retrospective review of a cohort of HIV positive individuals with bacterial diarrhea in the U.S. between 1992 and 2002, *C. difficile* was identified in 53.6% of the cases, with an incidence of 4.1 per 1000 person-years, see Figure 8.³⁰ In a prospective cohort evaluation of HIV inpatients in a tertiary care hospital in Chicago, risk factors for *C difficile* carriage include recent hospital admission (p=0.04), prolonged hospital stay (p=0.02), use of H-2 blocker while inpatient (p<0.05), treatment for PCP while an inpatient (p<0.05), and history of herpes virus (p=0.03) or opportunistic infections (p=0.04).³¹ This study was performed prior to the use of HAART. The relatively elevated incidence may be due to frequent antibiotic use or frequent hospitalization.

Salmonella, *Shigella*, and *Campylobacter*

In the same review of HIV positive individuals with bacterial diarrhea, *Shigella* and *Campylobacter* were identified each at approximately 14%, and *Salmonella* in 7.5%.³⁰ This study represents prevalence of these bacterial pathogens in the HAART-era. These bacteria have a higher incidence of intestinal infection, bacteremia, and prolonged or recurrent infections because of antibiotic resistance, alterations in mucosal immunity, or compromised immune function.^{32 33}

Mycobacterium sp.

Mycobacterium avium-complex complex (MAC) and *Mycobacterium tuberculosis* account for 3.6% of bacterial diarrhea.³⁰ Infection presents in those with depressed CD4, usually <50, causing systemic symptoms of malaise, fever, night sweats, weight loss, and diarrhea.^{32 33} Diarrhea occurs in 47% of those with disseminated MAC.³⁴ Diarrhea and malabsorption occur through blockage of the lymphatic system and involvement of the villi.^{25 35} See Figure 9. MAC used to be the most common cause of bacterial diarrhea in individuals with AIDS³⁶, but the incidence has decreased since the use of HAART and MAI prophylaxis.

MAC treatment is a prolonged course of combination antibiotics, usually a macrolide and ethambutol. Treatment continues for 12 months or until the CD4 is greater than 100 and then for 6 months. If the CD4 never rises above 100, then treatment is continuous.³⁷

Viral

Viral causes of diarrhea are common in those with and without HIV. Astrovirus, picobirnavirus, caliciviruses, and adenoviruses are more likely to be found in HIV-positive persons with diarrhea than without diarrhea.³⁸ However, these viruses and other common gastroenteritis causing viruses, including rotavirus and coronavirus, cause self-limiting, untreatable diarrhea. Cytomegalovirus is unique in that it causes prolonged symptoms and treatment ameliorates symptoms.

Cytomegalovirus (CMV) can infect the entire GI tract from mouth to anus causing inflammation, ulceration, and perforation. The most common manifestation is colitis-leading to fever and chronic watery, bloody diarrhea, abdominal pain, and occasionally necrosis and perforation.³⁹ CMV colitis usually afflicts those with CD4 counts <100/mm³ and accounts for up to 20% of the diarrhea in patients with AIDS.³³ Treatment is with ganciclovir or foscarnet followed by suppressive therapy.

HIV ENTEROPATHY AND GASTROINTESTINAL MALFUNCTION

HIV has been suggested to cause direct changes to intestinal mucosa. The term enteropathy has been used to describe pathogen negative diarrhea. However, it is impossible to completely rule out a pathogen association, thus this is a diagnosis of exclusion. Possible mechanisms include a direct effect by HIV to causing gastrointestinal malfunction and malabsorption. This is an area of continued research and discovery.

Knox et al evaluated the patterns of gastrointestinal dysfunction in an HIV-positive cohort enrolled in the Nutrition for Healthy Living Study.²⁰ This study included 671 HIV-positive men and women. As mentioned above, 45% of the cohort was on HAART, 40% of the cohort had diarrhea. Absorptive function was measured using a 25g D-xylose test (for carbohydrate absorption), a Sudan-III stain for fecal fat on a 100g fat diet (for fat absorption), and serum levels of albumin, vitamin B12, D-xylose, and folate. D-xylose and fat are absorbed primarily in the small intestine; vitamin B12 is absorbed in the ileum of the small intestine but requires intrinsic factor from the gastric parietal cells. 48% of participants had low D-xylose absorption, 4.1% had low serum vitamin B12, and 13% had fat malabsorption, see Table 4. Abnormal D-xylose absorption and borderline vitamin B12 absorption were more likely common with CD4 <200 cells/mm³ (p=0.46 and 0.003, respectively), while current diarrhea and fat malabsorption were just as likely regardless of CD4, suggesting an underlying enteropathy in HIV, see Table 6.

Sharpstone et al⁴⁰ evaluated gastric emptying, small bowel transit, absorption and permeability in a case-control study of 60 HIV-positive subjects with Stage IV AIDS (i.e. end-stage AIDS). A third of the patients were on retroviral therapy (zidovudine, zalcitabine

or didanosine) and 94% were on some type of PCP prophylaxis. Subjects provided a stool sample that was analyzed by for pathogenic bacteria, cryptosporidia, mycobacteria, ova and parasites, *C. difficile*, enteric viruses. Each subject with diarrhea and/or weight loss also underwent EGD with duodenal biopsy and sigmoidoscopy or colonoscopy with biopsy. Orojejunal transit time was measured using serum measurement of an oral 3-0-methyl-D-glucose solution as it is absorbed rapidly in normal jejunum. Orocecal transit was measured using a serum level of a metabolite of sulphasalazine that passes intact through normal small bowel lumen but is absorbed quickly in the cecum. The difference between these two transit times is the small intestinal (jejunal to cecal) transit time. Further, orojejunal transit time can be assumed to be the gastric emptying time. Small bowel absorption was measured using a urine sample for byproducts of an oral solution of 3-0-methyl-D-glucose, d-xylose, l-rhamnose and lactulose. To evaluate the validity of the above experiments and for small bowel bacterial overgrowth, six controls, six AIDS subjects, and six Crohn's disease patients received the test solutions of 3-0-methyl-D-glucose and sulphasalazine intraduodenally during endoscopy. All Crohn's patients had confirmed small intestinal bacterial overgrowth. Low levels of sulphasalazine metabolites prior to the expected cecal spike suggests bacterial metabolism. This pattern was seen in those with Crohn's but not in controls or AIDS subjects, see Figure 10. In those with AIDS, gastric emptying time was delayed ($p < 0.05$). Small bowel absorption was impaired as measured with D-xylose, L-rhamnose, and lactulose in all AIDS subjects, see Table 7 and 8. Small bowel transit time was decreased in 50% of those with AIDS and cryptosporidiosis, microsporidiosis, or pathogen negative diarrhea, but only in those with cryptosporidiosis was this significant against controls ($p < 0.0005$), see Figure 11. While delayed gastric emptying can cause bloating and early satiety, small intestine malabsorption or decreased transit time may lead to diarrhea. The limitations of this study include: only certain types of bacteria were evaluated for bacterial overgrowth, gastric emptying of solids was not measured, pathogen-negative diarrhea may not be an accurate term as only few causes were evaluated, it was not performed in the U.S., and it took place before HAART was used.

In an evaluation of fat malabsorption in HIV-positive individuals with chronic diarrhea, 95% of those not on HAART and 83% of those on HAART had fat malabsorption as measured by 24-hour stool specimen for fecal fat.⁴¹ There was no difference in the measure of fat in those with or without an identified stool pathogen, see Table 9.

In study evaluating for small bowel bacterial overgrowth by duodenal fluid culture performed in Birmingham, Alabama between 1995 and 1997, small bowel bacterial overgrowth was not common in those with AIDS, with or without diarrhea.⁴²

In a small study evaluating jejunal intrinsic autonomic function, biopsies from 11 HIV-infected homosexual males showed extensive damage to autonomic nerve fibers in the lamina propria.⁴³ This suggests a cause for small intestinal transit malfunction.

Moving onto the microscopic effects of HIV, recent studies show 1) an increased intercellular permeability by decreased electrical resistance in duodenal epithelium in HIV infected subjects, 2) cytoskeletal changes (tubulin depolymerization) in small bowel and colonic epithelial cells in HIV infected subjects, and 3) changes in cytosolic calcium (which is associated with cytoskeletal depolymerization and decreased epithelial resistance) by incubation of gp120 with intestinal cells.¹¹

Jejunal mucosal changes in those with HIV include decreased surface area to volume ratio, shortened villi, and normal crypt length with increased mitoses leading to an overall atrophy with epithelial hypoproliferation and dysmaturation of enterocytes.^{35 44 45} See Table 10 and Figure 12.

In support of direct effects of HIV on enteric mucosa, treatment has been shown to cause improvement of gastrointestinal symptoms, decreased apoptotic cells, and decreased tissue RNA after starting HAART. These effects are seen even after 7 days of treatment.^{11 46} The decrease in tissue RNA is in similar quantity to the decrease in plasma RNA. See Figure 13.

MEDICATION SIDE EFFECTS

As the treatment for HIV improved over the past few decades, patients were living longer and healthier lives. The incidence of infectious diarrhea decreased, however diarrhea continues to afflict patients.^{8 18 47} For many this adverse effect is unbearable and treatment must be changed.

Protease inhibitors frequently have GI upset and diarrhea as side effects. Ritonavir (norvir) alone has an incidence of diarrhea between 19-37% based on initial randomized double blind trials. The higher bracket of diarrheal incidence may be related to higher milligram dosing of ritonavir.⁴⁸ However, ritonavir is frequently combined with other protease inhibitors, though in low doses, to increase blood levels. A common combination is lopinavir and ritonavir (Kaletra). This combination tablet has an incidence of diarrhea of 24-26% as seen in two long-term randomized double-blind placebo-controlled trials.⁴⁹ Another common protease inhibitor, nelfinavir (viracept) has an incidence of diarrhea up to 32% in the first 24 weeks of treatment, based on randomized double blind trials.⁵⁰

The nucleoside analogues also cause diarrhea, Abacavir is frequently used either alone or in combination. Initial randomized double blind placebo-controlled trials with Ziagen (abacavir) show a 17% incidence of diarrhea.⁵¹ Didanosine (Videx) is believed to cause diarrhea by two mechanisms.⁵² The first can occur in up to 18% and is caused by the buffer in the preparation. Didanosine also causes pancreatitis in about 5% which can lead to steatorrhea.

MALNUTRITION

Malnutrition, weight loss and wasting are common in those with HIV.⁵³ This may be due to difficulty eating (esophagitis, altered taste perception, dysphagia), malabsorption, diarrhea, or increased catabolism. HIV-infected patients who lost more than 10% of their baseline weight had a six-fold increased in mortality ($p < 0.05$), including those on HAART.⁵⁴ In HIV patients that are losing weight, total energy expenditure is decreased and energy intake is decreased by up to 50% creating an overall energy imbalance.⁵⁵ Opportunistic infection increases the resting metabolic rate but decreases the physical activity energy expenditure, causing a net decrease in total energy expenditure.⁵⁶ Malnutrition can be treated by treating the underlying HIV as well as increasing protein and nutrient intake. Small, frequent meals consisting of high-protein, low-fat, and high-calorie foods are recommended to counter the increased catabolism.

DIAGNOSTIC ALGORITHM

Diagnosis is important, as many causes of diarrhea in HIV are treatable or reversible. Initial history and physical exam can provide clues into travel, animal exposure, sexual practices, diet, medications, and previous illnesses. CD4 count can help identify likely pathogens. Stool samples are examined for pathogenic bacteria (Salmonella, Shigella, Campylobacter), ova and parasites and *C. difficile* toxin. If these are negative, proceed to colonoscopy with or without esophagogastroduodenoscopy for biopsy for CMV, mycobacteria, HSV, adenovirus, protozoa, and fungi. Choice of endoscopy should be based

on the symptoms of the patient. Large volume, infrequent or nocturnal diarrhea with signs of dehydration suggests small bowel pathology while more frequent, small volume, bloody, mucousy diarrhea with abdominal pain but without signs of dehydration suggests colonic origin. Biopsies should be sent for bacterial, AFB, viral and fungal culture as well as examined with light microscopy for viral inclusion bodies, histoplasmosis, and with electron microscopy for microsporidia.^{57 58 59} Samples should also be sent for viral antigens.

CONCLUSION

Gastrointestinal symptoms, including diarrhea, are significant causes of morbidity and potential mortality in HIV in the USA. Because of this, the general practitioner who treats HIV positive patients should be aware of the various etiologies of diarrhea in HIV. Understanding the basics of HIV and how it affects the gastrointestinal mucosal immune system are necessary for this task. However, there is still many unanswered questions making future studies on the etiology, diagnosis, and treatment of diarrhea in HIV infected patients essential.

Figure 1: Normal jejunal mucosa. http://webanatomy.net/histology/digestive_histology.htm



Figure 2: Normal colonic mucosa. http://webanatomy.net/histology/digestive_histology.htm

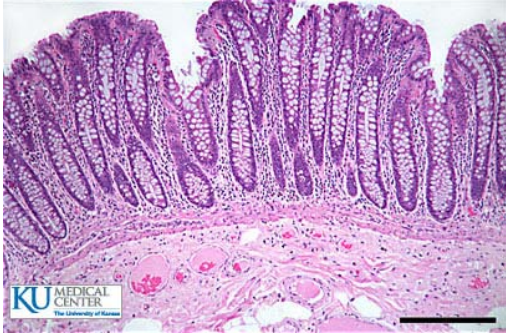


Figure 3: Peyer's patch. http://webanatomy.net/histology/digestive_histology.htm

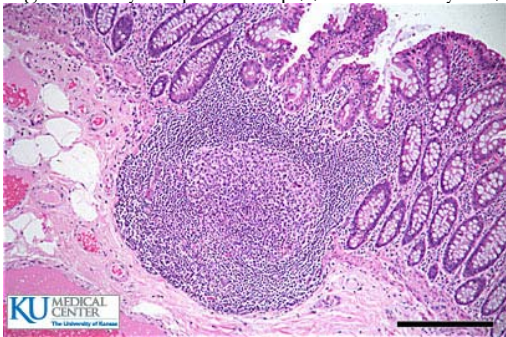


Figure 4: HIV particle. www.aegis.com/topics/basics/hivandaids.html

Organization of the HIV-1 Virion

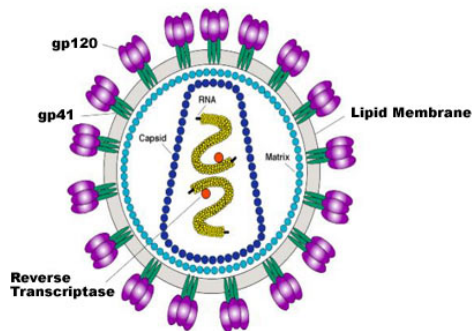


Figure 5: Proportion of study subjects with diarrhea. From Siddiqui et al.

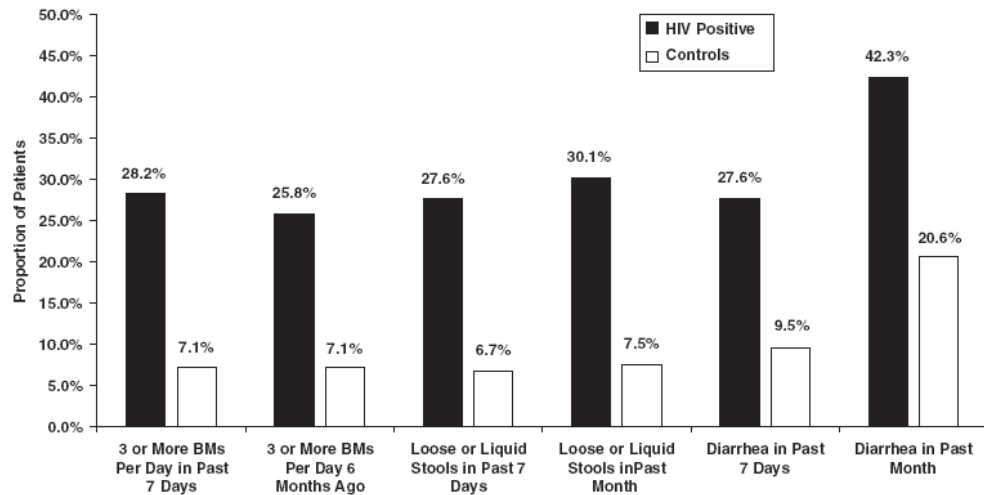


FIGURE 1. Proportion of patients with diarrhea among HIV-positive patients and control subjects. Diarrhea was significantly more common among HIV-positive patients than in control subjects according to several criteria ($P < 0.001$ for all comparisons between HIV-positive patients and control subjects). BMs indicates bowel movements.

Table 1: Percent of subjects with diarrhea according to demographic. From Siddiqui et al.

TABLE 2. Proportion of HIV-infected Patients With Diarrhea According to Select Demographic and Clinical Characteristics*

	No. Subjects	Proportion With Diarrhea (%)	<i>P</i>
Age, years			0.002
< 40	16	18.8	
40-49	54	18.5	
50-59	67	26.9	
60 and older	26	57.7	
Sex			0.61
Female	18	33.3	
Male	145	27.6	
Race/ethnicity			0.06
White, non-Hispanic	21	47.6	
Black, non-Hispanic	102	23.5	
Hispanic or Latino	35	25.7	
Others	5	60.0	
Education ≤ 12 y			0.23
No	66	33.3	
Yes	97	24.7	
Annual income \leq \$10,000			0.15
No	57	35.1	
Yes	106	24.5	
CD4 count, cells/mm ³			0.08
< 200	40	27.5	
200-350	35	42.9	
> 350	88	22.7	
HIV RNA undetectable			0.12
No	83	22.9	
Yes	80	33.8	
Any antiretroviral therapy			0.67
No	13	23.1	
Yes	150	28.7	
Nucleoside reverse transcription inhibitor use			0.46
No	15	20.0	
Yes	148	29.1	
Non-nucleoside reverse transcription inhibitor use			0.29
No	92	31.5	
Yes	71	23.9	
Protease inhibitor use			0.004
No	75	17.3	
Yes	88	37.5	

*Diarrhea was defined as ≥ 3 bowel movements per day within the last 7 d.

Table 2: Comparison of HRQOL in HIV-positive patients and control subjects. From Siddiqui et al.

TABLE 3. Comparison of HRQOL in HIV-positive Patients and Control Subjects*

	HIV-positive (n = 163)	Controls (n = 253)	<i>P</i>
Physical functioning	65.1 ± 30.4	83.9 ± 22.8	< 0.001
Role-physical	42.6 ± 43.5	78.5 ± 39.0	< 0.001
Bodily pain	63.7 ± 28.6	84.1 ± 23.0	< 0.001
General health	49.9 ± 23.1	74.8 ± 21.0	< 0.001
Vitality	47.6 ± 22.4	68.6 ± 25.9	< 0.001
Social functioning	60.2 ± 31.6	87.3 ± 24.1	< 0.001
Role-emotional	50.9 ± 44.8	81.6 ± 37.7	< 0.001
Mental health	62.0 ± 23.2	78.8 ± 21.1	< 0.001
Physical component summary scale	41.8 ± 10.9	50.7 ± 8.5	< 0.001
Mental component summary scale	43.5 ± 11.8	52.2 ± 11.7	< 0.001

*HRQOL was measured using the SF-36. Scores for each of the 8 domains range from 0 to 100, with higher scores indicating better HRQOL. The physical component summary and mental component summary scales are standardized using norm-based scoring to have a mean of 50 and a standard deviation of 10 in the general US population.

Table 3: Comparison of HRQOL in HIV-positive patients with and without diarrhea. From Siddiqui et al.

TABLE 4. Comparison of HRQOL in HIV-positive Patients With and Those Without Diarrhea*

	Diarrhea (n = 46)	No Diarrhea (n = 117)	<i>P</i>
General health	45.3 ± 19.9	53.4 ± 22.7	0.04
Physical function	45.8 ± 22.3	73.4 ± 24.2	< 0.001
Role function	19.6 ± 35.7	49.6 ± 48.5	< 0.001
Social function	39.6 ± 22.5	56.1 ± 28.4	< 0.001
Cognitive function	81.8 ± 20.9	78.6 ± 22.2	0.39
Pain	47.1 ± 28.4	72.6 ± 27.1	< 0.001
Mental health	61.8 ± 18.0	64.9 ± 23.0	0.38
Energy/fatigue	35.2 ± 18.0	53.2 ± 21.2	< 0.001
Health distress	44.8 ± 33.6	70.9 ± 24.0	< 0.001
Quality of life	41.3 ± 24.3	65.2 ± 23.2	< 0.001
Health transition	48.4 ± 25.5	58.3 ± 23.7	0.02

*Diarrhea was defined as ≥ 3 bowel movements per day within the last 7 d. HRQOL was measured using the MOS-HIV. Scores for each of the domains range from 0 to 100, with higher scores indicating better HRQOL.

Table 4: Percent of diarrhea and gastrointestinal malfunction in HIV-positive patients. From Knox et al.

Test	Total number	Abnormal				<i>p</i> Value: men vs women	Non- IVDU	% of non- IVDU	% of IVDU	Value: IVDU vs non- IVDU			
		Number	% of total	% of Men	% of men Women								
D-xylose (serum)													
<35 mg/dl	638	304	47.7	239	51.6	65	37.1	0.001	203	48.9	97	45.3	0.39
<30 mg/dl	638	193	30.3	150	32.4	43	24.6	0.055	130	31.3	60	28.0	0.40
History of liver disease	652	263	40.3	199	42.4	64	35.0	0.081	145	34.0	117	52.6	0.001
Diarrhea													
Current	653	254	38.9	196	41.6	58	31.9	0.022	176	41.2	76	34.2	0.083
Chronic	160	45	28.3	33	32.0	12	21.4	0.16	29	33.0	16	22.2	0.13
Severe	654	19	2.9	16	3.4	3	1.6	0.23	15	3.5	4	1.8	0.21
Serum vitamin B12													
<350 ng/L	632	142	22.5	112	23.9	30	18.4	0.15	106	25.5	35	16.9	0.016
<250 ng/L	632	26	4.1	18	3.8	8	4.9	0.65	22	5.3	4	1.9	0.049
Fecal fat	494	63	12.8	48	12.1	15	15.6	0.35	44	12.6	17	12.3	0.92
Stool pathogens													
Any (group 2)	499	61	12.2	59	14.7	2	2.0	0.001	54	15.5	7	4.9	0.001
Pathogenic	499	19	3.8	18	4.5	1	1.0	0.14	16	4.6	3	2.1	0.30
Albumin (<3.5 g/dl)	597	43	7.2	25	5.3	18	14.1	0.001	21	5.3	21	11.2	0.010
Serum folate (<3 μg/L)	413	3	0.7	3	0.9	0	0	1	2	0.7	1	0.8	1.00

p values are given from χ^2 tests.

Figure 6: Etiological categories of diarrhea by year. Light grey is opportunistic infection, white is medication associated or no cause, and black is non-opportunistic pathogens. From Call et al.

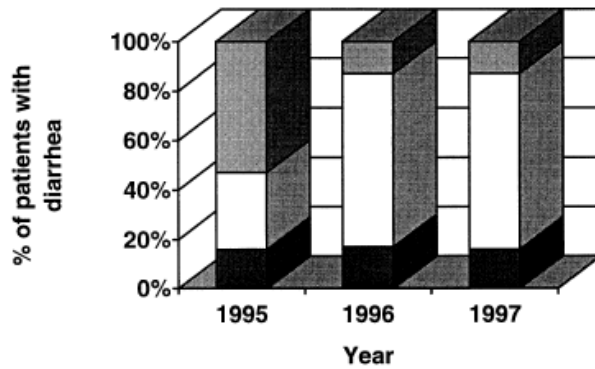


Figure 1. Etiological categories of diarrhea by year.

Table 5: Diarrhea cases and diagnoses by year. From Call et al.

Table 2. Diarrhea Cases and Diagnoses by Year of Study

	Year		
	1995	1996	1997
No. patients CD4 <200	239	287	306
No. case patients (% of patients CD4 <200)	19 (8.0)	30 (10.5)	31 (10.1)
Mean CD4 cell count	43	47	80
CMV	4	3	2
Cryptosporidium	5	0	1
MAC	1	1	1
Clostridium difficile	2	4	4
Giardia lamblia	1	0	1
Salmonella	0	1	0
Medication-associated	0	4	10
No diagnosis	6	17	12

CD4 = CD4 cell count; CMV = Cytomegalovirus; MAC = *Mycobacterium avium* complex.

Figure 7: Trends in the annual incidence of non-*C.diff*-associated diarrhea stratified by stage of HIV infection. From Sanchez et al.

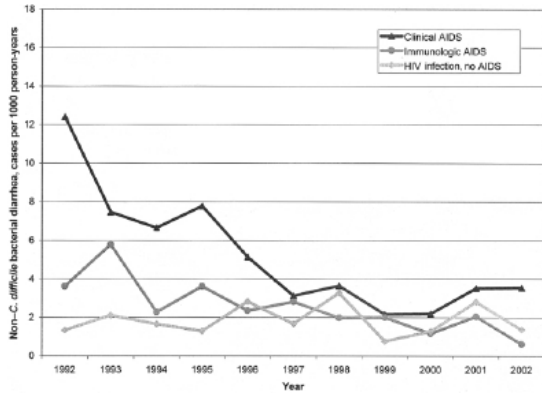


Figure 2. Trends in the annual incidence of other bacterial diarrhea i.e., not *Clostridium difficile*) among persons with HIV infection stratified by stage of HIV disease. Analysis includes data from 1992 through 2002 collected in >100 facilities in 9 US cities that participated in the Adult/Adolescent Spectrum of HIV Disease Project. Clinical AIDS was defined as any previous diagnosis of at least 1 AIDS-defining opportunistic infection, regardless of CD4⁺ cell count; immunologic AIDS was defined as any previous CD4⁺ cell count of <200 cells/mL or a CD4⁺ cell percentage of <14% but no clinical AIDS; and HIV infection without AIDS was defined as HIV infection not defined as immunologic or clinical AIDS.

Figure 8: Trends in *Clostridium difficile*-associated diarrhea stratified by stage of HIV infection. From Sanchez et al.

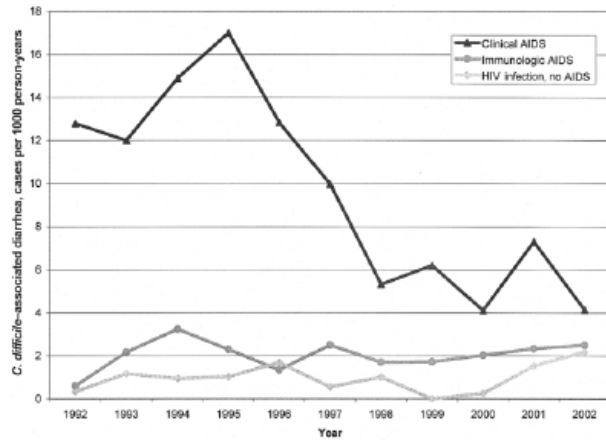


Figure 1. Trends in the annual incidence of *Clostridium difficile*-associated diarrhea (CDAD) among persons with HIV infection stratified by stage of HIV disease. Analysis includes data from 1992 through 2002 collected in >100 facilities in 9 US cities that participated in the Adult/Adolescent Spectrum of HIV Disease Project. Clinical AIDS was defined as any previous diagnosis of at least 1 AIDS-defining opportunistic infection, regardless of CD4⁺ cell count; immunologic AIDS was defined as any previous CD4⁺ cell count of <200 cells/mL or a CD4⁺ cell percentage of <14% but no clinical AIDS; and HIV infection without AIDS was defined as HIV infection not defined as immunologic or clinical AIDS.

Figure 9: A) H&E stain of jejunal epithelium infected with MAI. B) AFB stain of jejunal epithelium infected with MAI. From Owens et al

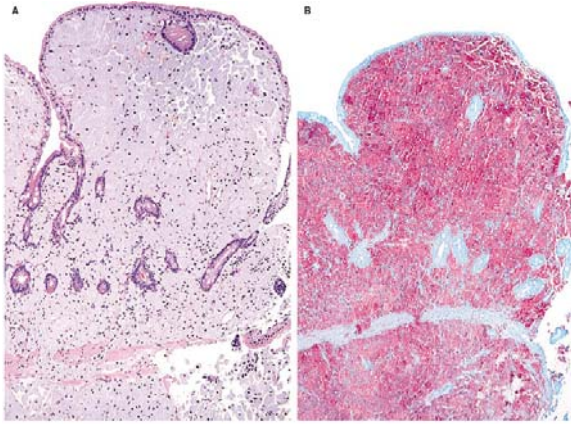


Figure 7. Low-power composite of *Mycobacterium Avium* complex in an AIDS patient. A. H&E-stained section mimicking the changes of Whipple's disease seen in Figure 5. B. AFB stain showing diffuse positivity.

Table 6: Prevalence of an abnormality of gastrointestinal function among those with AIDS, CD4<200, or diarrhea. From Knox et al.

Table 3. Prevalence of an Abnormality of Gastrointestinal Function Among Those With AIDS, CD4 <200, or Diarrhea

	n	AIDS	No AIDS	p Value	CD4 <200	CD4 >200	p Value	Diarrhea	No Diarrhea	P Value
D-xylose (<35 mg/dl)	638	50.2%	42.4%	0.061	52.6%	45.4%	0.094	50.6%	46.0%	0.26
D-xylose (<30 mg/dl)	638	34.1%	23.5%	0.006	35.8%	27.9%	0.046	32.5%	29.4%	0.41
Current diarrhea	653	41.8%	33.8%	0.044	43.2%	37.3%	0.17	NA		
Vitamin B12 (<250 ng/L)	632	4.7%	3.2%	0.39	5.9%	3.2%	0.11	2.5%	5.1%	0.11
Vitamin B12 (<350 ng/L)	632	23.6%	20.2%	0.33	30.1%	19.1%	0.003	22.2%	22.7%	0.90
Stool pathogen group 1	499	3.9%	3.8%	0.98	5.6%	3.0%	0.15	3.5%	3.9%	0.84
Stool pathogen group 2	499	10.5%	10.5%	0.86	11.3%	12.7%	0.67	9.1%	14.5%	0.073
Albumin (<3.5 g/d)	597	8.2%	8.2%	0.23	7.7%	6.8%	0.68	5.7%	8.3%	0.24

The number (n) is the total number of subjects with the gastrointestinal variable measured. Values are given as a percentage of those with or without AIDS, low CD4 count, or current diarrhea. NA = not applicable.

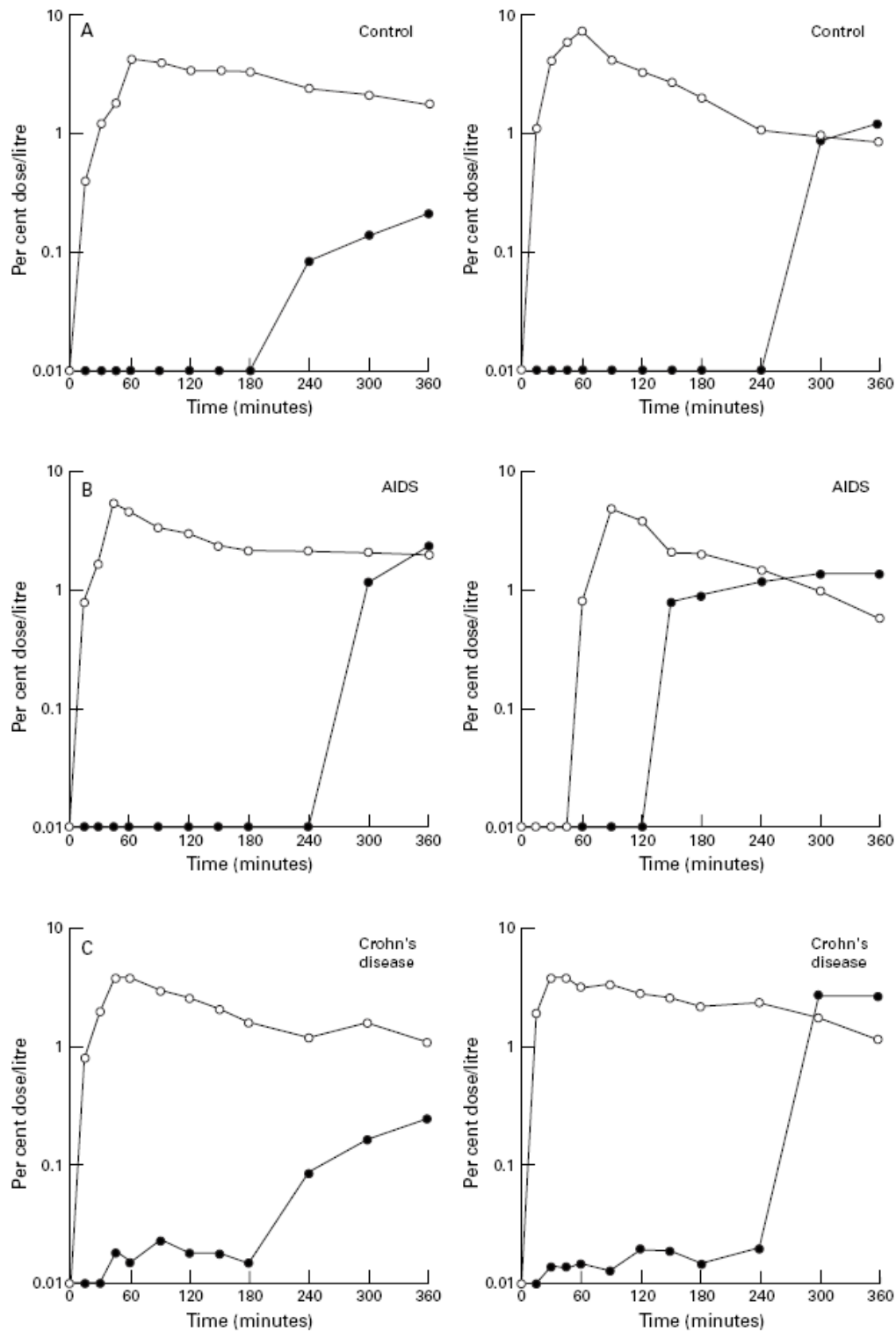


Figure 1 Representative permeation profiles of 3-O-methyl-D-glucose (open circles) and sulphapyridine (closed circles) after ingestion of the monosaccharide and sulphasalazine in two control subjects (A), two patients with AIDS (B), and two patients with Crohn's disease associated with small bowel bacterial overgrowth (C).

Figure 10: Representative profiles of 3-O-methyl-D-glucose (open circles) and sulphasalazine metabolites (closed circles) after ingestion in A) control subjects, B) AIDS subjects, and C) Crohn's subjects. From Sharpstone et al.

Table 7: Gastric emptying of a liquid in AIDS. From Sharpstone et al.

Table 1 Gastric emptying of a liquid in AIDS

	Median time (range) in minutes of first appearance of 3-O-methyl-D-glucose in serum
Controls	15 (15-30)
AIDS, well	22.5 (15-60)*
AIDS, weight loss	30 (15-60)†
Pathogen negative diarrhoea	30 (15-45)‡
CMV colitis	30 (15-90)*
Microsporidiosis	15 (15-45)*
Cryptosporidiosis	15 (15-90)*

Statistical analysis performed by the Mann-Whitney test.

*Differed significantly from controls (p<0.05).

†Differed significantly from controls (p<0.005).

‡Differed significantly from controls (p<0.001).

CMV, cytomegalovirus.

Table 8: Small intestinal absorption and permeability in AIDS. From Sharpstone et al.

Table 2 Small intestinal absorption and permeability in AIDS

	Number	CD4 count (cells ×10 ⁶ /l)	Body mass index (weight/ height ²)	3-O-m-D-glucose (% dose)	D-xylose (% dose)	L-rhamnose (% dose)	Lactulose/ L-rhamnose
Controls	20		26 (2)	47.5 (11.1)	31.7 (7.3)	12.8 (2.6)	0.03 (0.01)
AIDS, well	6	112 (146)	21 (3)*	33.4 (3.0)	23.3 (3.0)‡	5.0 (1.4)‡	0.04 (0.05)
AIDS, weight loss	11	9 (9)	18 (2)‡	31.5 (17.2)	12.5 (4.2)‡	3.4 (1.3)‡	0.14 (0.12)‡
Pathogen negative diarrhoea	10	25 (29)	19 (3)†	36.3 (14.6)	20.5 (12.1)‡	4.7 (2.3)‡	0.15 (0.09)‡
CMV colitis	12	35 (41)	20 (4)‡	39.6 (14.3)	15.5 (6.3)‡	4.2 (1.5)‡	0.20 (0.14)‡
Microsporidiosis	11	37 (52)	19 (3)‡	31.7 (16.7)	13.4 (7.1)‡	3.2 (2.1)‡	0.09 (0.06)‡
Cryptosporidiosis	10	19 (15)	18 (4)*	33.4 (12.4)	15.9 (7.0)‡	3.7 (1.7)‡	0.15 (0.14)‡

Values presented are mean (SD).

A one way ANOVA was showed significant (p<0.0001) differences in absorption-permeability data between the groups, apart from the 3-O-methyl-D-glucose group.

*Differed significantly from controls (p<0.05; Student's t test using Bonferroni's correction).

†Differed significantly from controls (p<0.01).

‡Differed significantly from controls (p<0.001).

CMV, cytomegalovirus.

Figure 11: Jejuno to caecal transit times in patients with AIDS. Upper and lower limit of normal represented by horizontal lines. From Sharpstone et al.

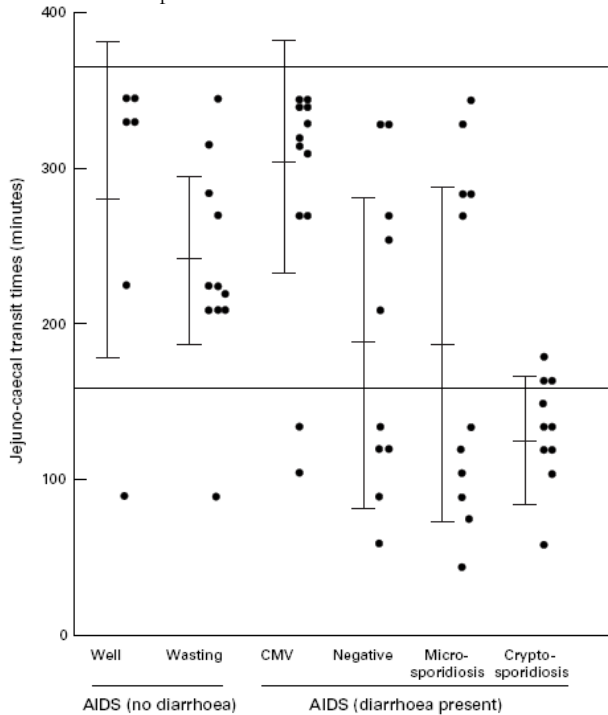


Figure 2 Individual jejuno to caecal transit times in the patients with AIDS. The two horizontal lines represent the upper and lower normal range as obtained from the 20 control subjects. Horizontal bars represent mean values and the vertical bars represent SD.

Table 9: Amount of fecal fat and stool weight in HIV-patients. From Poles et al.

	Non-HAART Patients		HAART-Treated Patients	
	Pathogen Identified	No Pathogen Identified	Pathogen Identified	No Pathogen Identified
N	12	0	3	0
Fecal fat	37,8 ± 48,4	31,0 ± 18,5	35,8 ± 45,2	48,9 ± 98,2
Stool weight	546,8 ± 154,8	1065 ± 530,3	1105 ± 578,7	710,9 ± 631,5

Figure 12: Patterns of small intestinal transformation. HIV follows the atrophy pattern of crypt transformation. From Zeitz et al.

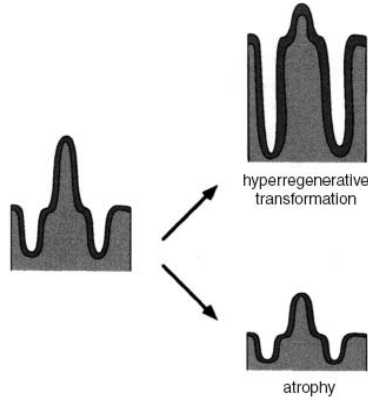


FIGURE 1. Patterns of small intestinal transformation to various forms of stress: Villous atrophy is either associated with a hyperregenerative increase in crypt cell mitoses leading to crypt elongation (e.g., in gluten-sensitive enteropathy), or it results from hyporegeneration, that is, reduced mitotic rate with shortened crypts (as seen in starvation or total parenteral nutrition).

Table 10: Gastrointestinal changes due to HIV infection. From Zeitz et al.

TABLE 1. HIV/SIV enteropathy^a

	Late Phase of Infection (Humans)	Early Phase of Infection (Nonhuman Primates)
CD4+ T cells	↓↓	↓↓
CD8+ T cells	↑↑	↑↑
Activation of CD8+ T cells	(↑)	↑↑
Villous height	↓	↓
Crypt depth	↔	↔
Crypt cell proliferation	(↓)	↑
Brush-border enzyme activity	↓↓	?

^aSummary of the main findings in HIV infection in humans and in the early phase of SIV infection in nonhuman primates (up to 12 weeks): The relative proportions of lamina propria T cells were investigated by flow cytometry of isolated cells. Mucosal architecture was studied by microdissection and morphometry.

Figure 13: Change in tissue RNA before and 7 days after HAART in A)rectal biopsies and B)plasma. From Kotler et al.

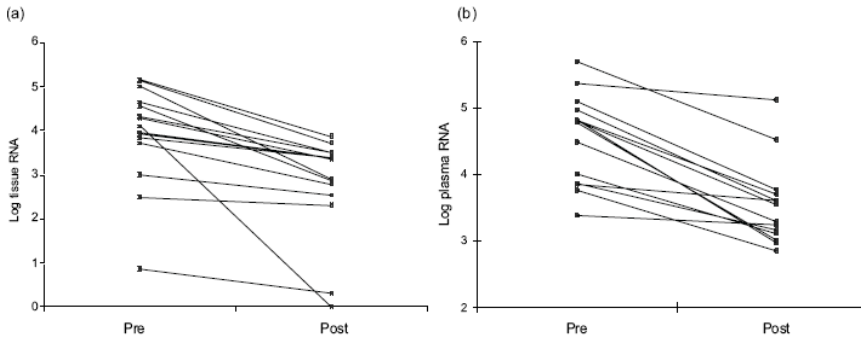


Fig. 8. HIV-RNA polymerase chain reaction studies in pairs from 15 subjects, obtained immediately before initiating combination antiretroviral therapy and 7 days later. (a) Rectal biopsies. The mean tissue RNA content fell by 1.14 log ($P < 0.001$). Adapted from Kotler et al. [37]. (b) Plasma samples. The mean plasma RNA content fell by 0.95 log ($P < 0.001$).

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