AIDS and the Gastrointestinal Tract

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Human immunodeficiency virus (HIV) infection was first recognized in the United States in the summer of 1981[1], when the Centers for Disease Control and Prevention (CDC) reported the unexplained occurrence of *Pneumocystis carinii* pneumonia. HIV has caused a global pandemic, with the number of infected individuals estimated by WHO at approximately 33.4 million worldwide at the end of 1999.[2] In Thailand, the first case was reported in 1984 and there are presently around 1 million HIV infected persons and 99,555 persons with full blown AIDS at the end of 1999[3], according to the Division of Epidemiology, Ministry of Public Health, Thailand. HIV disease is characterized by progressive immunodeficiency state associated with depletion and defect of CD4+ T cells. Advanced or full blown HIV disease is referred to as acquired immunodeficiency syndrome (AIDS). When the CD4+ T-cell count falls below a certain critical level, usually 200/uL, the infected individual becomes highly susceptible to a number of opportunistic infections and neoplasms.

Gastrointestinal disease is one of the most common manifestations of HIV infection.[4,5] The gastrointestinal tract contains abundant quantity of lymphoid tissue and is likely to function as a reservoir of HIV infection, a site of profound immune dysregulation, and a target for opportunistic infection (OI) and malignancy.[4] Almost all AIDS patients will have gastrointestinal symptoms sometimes during the course of their illness.

The common GI symptoms have been classified as:

1. Chronic diarrhea
2. Sore mouth/ Sore tongue
3. Dysphagia/ Odynophagia
4. Abdominal pain/ Nausea/ Vomiting
5. Upper/ Lower GI bleeding
6. Proctitis/ Anorectal pain syndrome
7. Wasting syndrome
8. Hepatobiliary manifestation (jaundice, hepatomegaly, abnormal liver function tests)

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CHRONIC DIARRHEA

Chronic diarrhea is the most common GI symptom especially in full blown AIDS.[6-9] Data from Swiss HIV cohort study showed the incidence of chronic diarrhea in HIV to be 14.2 per 100 persons per year.[7] It is caused by infectious agent that may be due to bacteria, fungus, parasite, or virus (include HIV itself). This symptom can be continuous or intermittent, can persist for more than 3 months, and with significant weight loss (slim disease). Prior to further investigation, a careful history should be obtained. Although rarely diagnostic, history can assist in pinpointing the portion of the gastrointestinal tract most severely involved. Critical factors in the clinical assessment are the CD4 cell count, history of recent antibiotic use, and establishing whether the diarrhea is acute or chronic. Physical examination is less often helpful, while diagnostic studies can be obtained judiciously in a stepwise fashion. In developed countries, aggressive investigation can lead to causes in only 70-85 percent and 10-40 percent of cases have more than one organisms.[10-12] The most common causes of diarrhea in these countries are cryptosporidium, *mycobacterium avium complex* (*MAC*) and microsporidium.[12,13] In Thailand, the causes are found in 56-65 percent and 15.5-17 percent had more than one organism.[14,15] The most common causes of diarrhea are cryptosporidium, microsporidium, *mycobacterium tuberculosis*, salmonella, *CMV* and *MAC*, respectively as shown in table 1.[11,14,17] The prevalence rate of chronic diarrhea caused by giardia or *MAC* is very high in two recent studies.[18,19] Investigations include routine stool examinations looking for parasite larva, egg, stool staining for acid fast, modified acid fast, stool culture, electron microscopic study for microsporidia and assay for *clostridium difficile* toxin. Diagnostic step evaluation is as in table 2.[20,21] Endoscopy should be done in some cases with persistent diarrhea. Esophagogastroduodenoscopy with duodenal aspiration, small bowel biopsy should be performed to look for strongyloid, *giardia lambia*, cryptosporidium, microsporidium, and histoplasmosis or *MAC*.

Sigmoidoscopy and/or colonoscopy with biopsy to look for *CMV*, Kaposi's sarcoma (KS). Biopsies should be taken of any abnormal appearing mucosa or otherwise randomly from rectal mucosa. If stool evaluations and flexible sigmoidoscopy are non-diagnostic, an alternative approach is to proceed with colonoscopy and or upper endoscopy but these latter investigations are not usually performed. Trial of empiric antibiotics may include a quinolone and metronidazole for 7-10 days to treat possible small bowel overgrowth, culture-negative Campylobacter, *Entamoeba histolytica* (*E. histolytica*) or Giardia. Cotrimoxazole can be tried for 2-3 weeks to treat Isospora.[22]

SORE MOUTH AND SORE TONGUE

These symptoms are common but not usually the presenting symptoms. These can be found in early symptomatic HIV infection with increasing frequency in full blown AIDS. The causes of sore mouth and sore tongue are as in table 3.

Table 1 : Comparison of pathogens causing diarrhea between developed countries and Thailand.

Pathogens	Developed countries[11,16,17]	Thai data of HIV with chronic diarrhea	
		Data A (45 patients[14])	Data B (91 patients[15])
Protozoa			
- Cryptosporidium	15-23	20	25
- Isospora	2	ND	8
- Microsporidia	20-30	2.2	29
-- *E. histolytica*	5-10	ND	0
- Giardia	ND	4.4	5
Bacteria			
- Salmonella	5	15.5	ND
- Shigellla	5	ND	ND
- Campylobacter	10	2.2	ND
- *Clostridium difficile*	0-7	ND	ND
- *M. tuberculosis*	3-5	17.8	ND
- *M. avium complex*	6	6.6	ND
Virus			
- *Cytomegalovirus*	12	11.1	ND
- *Herpes simplex*	5-10	ND	ND
Parasite			
- Strongyloid	ND	4.4	5
Multiple pathogens	10-40	15.5	ND
No pathogen	15-30	35.6	ND

ND No data

* 14 Thai data studied during June 1994-December 1994.

**15 Thai data studied during January 1994-June 1997.

Oral candidiasis is the most common opportunistic infection in *HIV* infection and should make one think of *HIV* testing.[23] Symptoms include sore mouth, sore tongue and odynophagia if the patient has esophagitis. Physical findings include white plague in oral cavity (oral thrush), tongue, uvula and soft palate. Good response occurs with mycostatin or ketoconazole in oral suspension or troche forms but can recur.[24]

Oral hairy leucoplakia may be associated with *epstein-barr virus* (*EBV*) but most cases are asymptomatic and can spontaneously disappear.[1]

Table 2: Diagnostic evaluation of patients with AIDS who have diarrhea.

Step 1 :

- Stool examination (direct, concentrated or both) for parasites using saline, iodine, trichrome, acid fast strains
- Stool culture for salmonella, shigella, campylobacter at least 3 times and assay for *Clostridium difficile* toxin

Step 2 :

- Gastroduodenoscopy and colonoscopy to inspect tissue and to obtain biopsy specimens and luminal material
- Duodenal biopsy specimens, culture for *CMV* and mycobacterium
- Colonic biopsy specimens, culture for *CMV*, adenovirus, mycobacteria, and *herpes simplex*
- Biopsy specimens, stain with hematoxylin-eosin for protozoa and viral inclusion, with methenamine silver or giemsa for fungi, and with acidfast for mycobacteria
- Duodenal fluid specimen examined as above for parasite

Step 3 :

- Biopsy specimens, examine by electron microscopy for microsporidia (duodenal tissue) and adenovirus (colonic tissue)

In symptomatic cases, topical tretinoin or antiretroviral medication can be given.

DYSPHAGIA AND ODYNOPHAGIA

These are common symptoms and there are many causes as in table 4. Approximately one third of patients with AIDS will develop dysphagia or odynophagia at some point in the course of their disease.[25-27]

Esophageal candidiasis is easily diagnosed in those patients with oral candidiasis and odynophagia.[28] It's prevalence is approximately 42-79 percent[26,29] and usually is seen in patients with a CD_4 count < 200/mm^3, with 90 percent of patients having a CD_4 count < 100/mm^3.[30] However, 18 percent of patients with esophageal candidiasis did not have oral thrush.[28] Typical radiological or endoscopic findings are multiple plaque like lesions that may be focal and discrete or confluent. When involving the entire esophagus, a shaggy appearance resembling ulcerations may result. Systemic treatment with ketoconazole or azole group of antifungal drugs is indicated. Nonsystemic antifungal agents such as clotrimazole and nystatin are not very effective and should be reserved for the treatment of oropharyngeal diseases.[28]

CMV is the most common viral infection of the esophagus in HIV infected patients and causes esophagitis and ulcer. It is seen almost

Table 3 : Causes of sore mouth and sore tongue in AIDS.

Oral candidiasis
Oral hairy leucoplakia
Herpes simplex of perioral and oral cavity
Apthous ulceration
Gingivitis/Stomatitis
Dental abscess
Kaposi's sarcoma of oral cavity
Intraoral warts

exclusively when CD4 count <100/mm^3.[28] Typical findings include one or more discrete and extensive esophageal ulceration which large and deep.[30] Typical histopathology shows viral cytopathic effects in mesenchymal or endothelial cells (inclusion bodies). Systemic treatment with ganciclovir or foscarnet is indicated. The relapse rate of *CMV* esophagitis is approximately 50 percent.[31] The longterm maintenance therapy with gangciclovir is not routinely recommended unless there is co-existent retinitis.

HIV or idiopathic esophageal ulcer is common in HIV infected patients but this diagnosis depends on ruling out another cause especially *CMV* infection. Typical finding is a large painful ulcer and mimics other causes of ulcerative esophagus. Corticosteroids or thalidomide can be used. Oral corticosteroids therapy with prednisolone at 40 mg per day tapering 10 mg per week for a one month treatment course and the response is

Table 4 : Causes of dysphagia and odynophagia in AIDS.

INFECTION		
	FUNGUS	: Candida esophagitis
		Esophageal histoplasmosis
	VIRUS	: *CMV* esophagitis and ulcer
		HSV esophagitis and ulcer
		EBV esophageal ulcer
		HIV esophageal ulcer
	MYCOBACTERIUM	: *M. tuberculosis*
		M. avium complex
	PROTOZOA	: Cryptosporidium
		Pneumocystis carinii
NEOPLASM		: Kaposi's sarcoma
		Lymphoma
OTHERS		: Drug induced esophagitis and ulcer esp. AZT
		Acid-peptic disease eg. reflux esophagitis

Table 5 : Causes of abdominal pain in AIDS.

Recurrent abdominal pain

- Peptic ulcer disease
- Pancreatitis[33-36] ;

  Drugs induced eg. DDI, ganciclovir, pentamidine
- Disseminated infections eg. TB, crptococcosis, histoplasmosis

Severe abdominal pain with sign of peritonitis

- Acute appendicitis
- GI perforation from *CMV*, TB
- Acalculous cholecystitis
- Gangrene bowel

Abdominal pain with sign of obstruction

- GI lymphoma
- Kaposi's sarcoma

Abdominal pain with mass[37]

- Lymphoma
- Kaposi's sarcoma
- TB abdomen with TB retroperitoneal node

usually dramatic with most patients having significant amelioration of pain within several days.[32]

ABDOMINAL PAIN/ NAUSEA/ VOMITING

Abdominal pain in HIV infection can present as an acute or chronic condition. Severe acute abdominal pain may be a presenting symptom or occurs simultaneously with other symptoms. Nausea/ vomiting can present simultaneously with other symptoms such as persistent diarrhea, gastritis and esophagitis. These symptoms are caused by the same as those in immunocompetent or opportunistic infections or neoplasm as in table 5.

In Thailand, tuberculous infection is common and is a common cause of abdominal pain in HIV infected patients. Depletion of CD_4 cells results in markedly enhanced susceptibility to tuberculosis and to an increased frequency of extrapulmonary manifestations.[38] The most common intraabdominal site of involvement is the intraabdominal lymph nodes, spleen and peritoneum.[38] Clinical features are fever, chills, night sweats, weight loss and extraabdominal lymphadenopathy. Hematogenous dissemination of *M. tuberculosis* was documented by positive hemoculture in 74 percent.[38] Gastric, esophageal and pancreatic tuberculosis in HIV infected

patients were reported.[39,40] Treatment regimen is the same as in the immunocompetent host.

UPPER/ LOWER GI BLEEDING

These problems are of low incidence, less than 1 percent, and the causes are not different from the immunocompetent.[41-43] HIV associated upper GI bleedings can be caused by candida esophagitis, *CMV* esophagitis and gastritis, *HSV* esophagitis and gastritis, Kaposi's sarcoma and lymphoma. HIV associated lower GI bleedings can be caused by *CMV* colitis, salmonella enteritis, shigella enterocolitis, *E. histolytica* colitis, Kaposi's sarcoma and lymphoma. Diagnostic evaluation and treatment are the same as in immunocompetent by using endoscopy.

PROCTITIS/ ANORECTAL PAIN SYNDROME

These problems are common especially in homosexual persons. The main causes are sexually transmitted diseases such as gonorrhea, *herpes simplex*, lymphogranuloma venerum and condyloma.[44,45] Other causes are *E.histolytica*, giardia, chlamydia, salmonella, shigella, *M. tuberculosis*, *CMV*, anal fissure, hemorrhoids and rectal Kaposi's sarcoma. Treatment depends on the cause.

WASTING SYNDROME

Wasting syndrome is the involuntary loss of more than 10 percent of base-line body weight in combination with diarrhea, weakness and or fever.[46] It is an AIDS defining condition and one of the most devastating aspects of AIDS that leads to morbidity and mortality.[47-49] Many factors are likely to be involved in the pathogenesis.[47-51] Firstly, the intake of energy may be compromised by anorexia due to disease, the side effects of drug treatment, upper gastrointestinal disease, malabsorptive enteropathy, gastrointestinal infection include HIV itself, that interferes with the absorption of nutrients. Secondly, metabolic derangement by many cytokines such as tumor necrosis factor (TNF), interleukin-1, interleukin-6 and interferons or secondary opportunistic infections that cause increased resting energy expenditure. Malabsorptive enteropathy can be found with or without diarrhea and is not correlated with morphological mucosal change of small intestine.[52] Treatment include getting rid of opportunistic infection, nutritional supplement, exercise, appetite stimulating drugs, cytokine modulating drugs and antiretroviral drugs.[51,53,54]

HEPATOBILIARY MANIFESTATIONS (JAUNDICE, HEPATOMEGALY, ABNORMAL LIVER FUNCTION TESTS)

Hepatobiliary manifestations are common in HIV infected patients and can be found in 66-90 percent of especially advanced disease. Opportunistic infections and neoplasm of liver in HIV are usually found when the CD_4 count <200/ mm^3 except *M.tuberculosis* and Kaposi's sarcoma[55] which could be found with higher CD_4 count. The common presentation includes jaundice, hepatomegaly and abnormal liver function tests.

JAUNDICE

Jaundice is a common manifestation in AIDS and has different causes from immunocompetent person.The common causes of jaundice are drugs, viruses, bacteria or biliary abnormalities.[56] Drugs include many groups of antiretroviral and anti-infective drugs. Many drugs cause different clinical and liver histopathology as in table 6. Viral hepatitis A, B, C and D can cause jaundice as in immunocompetent. CMV, HSV, adenovirus and some bacteria such as salmonella, microsporidia can also cause jaundice. HIV infected person has increased risk to infection and septicemia from salmonella.[57] Some AIDS patients infected with salmonella can present with severe colitis or fever, jaundice with increased transaminases level of up to 10 times as drug or viral induced hepatitis.[58] The common biliary abnormality that causes jaundice is HIV cholangiopathy.

HEPATOMEGALY

Hepatomegaly is one of the most common findings in HIV infected persons and can be detected in 60-73 percent on physical examination and 84 percent on autopsy.[59] This can be divided into 2 types, diffuse or focal. Diffuse hepatomegaly may be caused by fatty liver, opportunistic infections or neoplasm especially lymphoma.[60] Focal hepatomegaly may be caused by lymphoma, Kaposi's sarcoma or tuberculous liver abscess.[60] Liver is the most common extranodal involvement of non-Hodgkin lymphoma and is commonly found with intraabdominal lymph nodes enlargement.[55]

ABNORMAL LIVER FUNCTION TESTS

Abnormal liver function tests are common problems in HIV infected person that include increased transaminases or alkaline phosphatase but are often asymptomatic. Abnormal transami-

Table 6 : Liver histopathology of common drugs induced in HIV infected person.

Drugs	Hepatocellular	Cholestasis	Granuloma
Trimethoprim-Sulfamethaxazole	++		
Ketoconazole	++		
Isoniazide	++		
Rifampizine		+	
Zidovudine (AZT)		+	
Pentamidine	+		
Diphenylhydatoin	+		+

nases may be caused by fatty liver, drugs induced or chronic viral infections.[61] High alkaline phosphatase may be caused by infiltrative diseases, space taking lesions with tumor or abscess, obstruction (HIV cholangiopathy by CMV, cryptosporidium or MAC), and nonspecific that may be related to drugs or sepsis.[62,63] Infiltrative diseases include opportunistic infections such as tuberculosis, cryptosporidium, histoplasmosis, *penicillium maneffei*, peliosis hepatis or lymphoma.[60] *Penicillium marneffei* infection is common in Thailand especially in the north and the northeast.[64] *Penicillium marneffei* is present in 8.7 percent of Thai HIV infected patients who had high alkaline phosphatase and those infected with *Penicillium marneffei* usually have skin lesions as well.

CONCLUSION

AIDS can involve any organ system including the gastrointestinal tract. Almost all AIDS patients will have gastrointestinal symptoms sometime during the course of their illness. The common GI symptoms include chronic diarrhea, sore mouth, sore tongue, dysphagia, odynophagia, abdominal pain, nausea, vomiting, upper or lower GI bleeding, proctitis, anorectal pain syndrome, wasting syndrome and hepatobiliary manifestation (jaundice, hepatomegaly, abnormal liver function tests). When the CD4+ T-cell count falls below a certain critical level, usually 200/uL, the infected individual becomes highly susceptible to a number of opportunistic infections and neoplasm. Prior to further investigation, a careful history should be obtained. Although rarely diagnostic, history can assist in pinpointing the portion of the gastrointestinal tract most severely involved. Critical factors in the clinical assessment are symptoms and CD4 cell count which is indicative of opportunistic infections or neoplasm. The treatment of these problems can prolong survival and improve the quality of life.

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