

Diarrhea in HIV Infection

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ABSTRACT

During the last decade, there has been an increase of immunocompromized patients all around the world; that mostly due to pandemic of Human Immunodeficiency Virus (HIV) infection. Chronic diarrhea as one of common symptoms in patients with HIV infection has different etiology compared to immunocompetent patients. Initial approach of diarrhea in HIV infection may be conducted by evaluating the temporal relationship between the development of diarrhea and the administration of antiretroviral, especially the protease inhibitor agents; which is then followed by fecal analysis/examination for pathogenic bacteria and protozoa as well as endoscopy examination.

Biopsy examination of intestinal mucosa is necessary for HIV enteropathy or diarrhea due to microsporidia, which is confirmed further by electron microscopy. The etiology of chronic diarrhea in HIV patients may also different, depend on the cluster of differentiation count value of all patients. Based on such differences, it is necessary to have adequate approach, recognition and understanding in the management of chronic diarrhea, especially for HIV patients.

Keywords: *diarrhea, infection, HIV*

INTRODUCTION

During the last decade, there has been an increase of immunocompromized patients all around the world; that mostly due to pandemic of Human Immunodeficiency Virus (HIV) infection. These patients have high risk of gastrointestinal infection, either by pathogenic or opportunistic microorganisms. Such microorganisms may be virus, bacteria, fungal, or protozoa. The symptoms of gastrointestinal infection may vary in such patient group, but commonly is diarrhea and difficulty in swallowing (symptoms of esophagitis).¹

Increased number of patients with HIV infection in developing countries is caused by poor hygiene, inadequate clean water supply and difficult access for treatment. Patients frequently are afflicted by gastrointestinal complication which will become more severe with the decrease of Cluster of Differentiation (CD4) count.² Until the end of March 2005, there has been 6,789 cases of HIV or Acquired Immune Deficiency Syndrome (AIDS) noted in Indonesia. Such number, in fact, is far under the real number since the Department of Health, Republic of Indonesia in 2002 has estimated that there are 90,000–130,000 of Indonesia people who has been infected by HIV.³ Data from WHO (UNAIDS 2007) until December 2007 has estimated that there are 33.2 million people in all around the world who has been infected by HIV.¹

Chronic diarrhea as one of common symptoms in patients with HIV infection has different etiology compared to immunocompetent patients. The etiology

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of chronic diarrhea in HIV patients may also differ, depend on the CD4 of patients.^{4,5} Based on such differences, it is necessary to have adequate approach, recognition and understanding in the management of chronic diarrhea, especially for HIV patients.

DEFINITION AND ETIOLOGY

Diarrhea is regarded as chronic when the diarrhea occurs more than 15 days. Other literature indicates such term when the diarrhea has been occurred more than 1 month.^{6,7,8} The cause of chronic diarrhea vary and resulting from not only by intestinal disorder, but also by endocrine disorder, malignancy, liver and pancreas disorder, infection, etc. In developing countries, the most common etiology for chronic diarrhea is infection. About 10-15% of etiology for chronic diarrhea is unknown. Diarrhea in patients with positive HIV infection, with or without AIDS, is caused by intestinal infection in 75-85% cases.^{6,7}

THE EFFECT OF HIV INFECTION ON GASTRO-INTESTINAL IMMUNE SYSTEM

HIV mainly brings infection to CD4 or T helper lymphocytes; and along with time, the CD4 amount will decrease. CD4 has a central role in organizing the body immune system. Although CD4 has role in cellular and humoral immunity but the damage is mainly occur on the cellular immune system. Overall, HIV infection causes immunity disorder in the patients with such infection.⁹

In the gastrointestinal tract itself, there are some types of immune system; one of them is natural immune system which has non-immunogenic characteristic. In the gastrointestinal tract, such immune system is a physiochemical barrier which can eliminate, inactivate, and cleanse pathogenic substances and various microorganisms. Such barrier includes gastric acids, gastrointestinal enzymes, bile acid, lysozymes, intestinal mucus, not to mention the normal peristaltic, normal intestinal flora and epithelial of intestinal mucosa itself, which has tight junction that hardly to be penetrated during intake. In patients with AIDS, there is a defect in one or more of the aforementioned factors; therefore, they are very vulnerable against the attack of pathogenic agents.^{9,10}

A study conducted by Blumberg et al demonstrated that in patients with CD4 200/mm³, there was 28.9% chronic diarrhea and 15.7% acute diarrhea. This study indicates that diarrhea may occur in patients with HIV, even not in the late stages. This may be caused by regional immunosuppression on the gastrointestinal tract. It has been known that there is a decrease of CD4 level in gastrointestinal mucosa; however, the peripheral CD4 level is quite high. It explains why in patients with HIV with a relatively high CD4 level can still have diarrhea episodes.^{4,9}

THE APPROACH TO MANAGE DIARRHEA IN HIV INFECTION

In patients with chronic diarrhea and HIV positive, it is necessary to perform an evaluation to determine the cause of diarrhea, as follows:

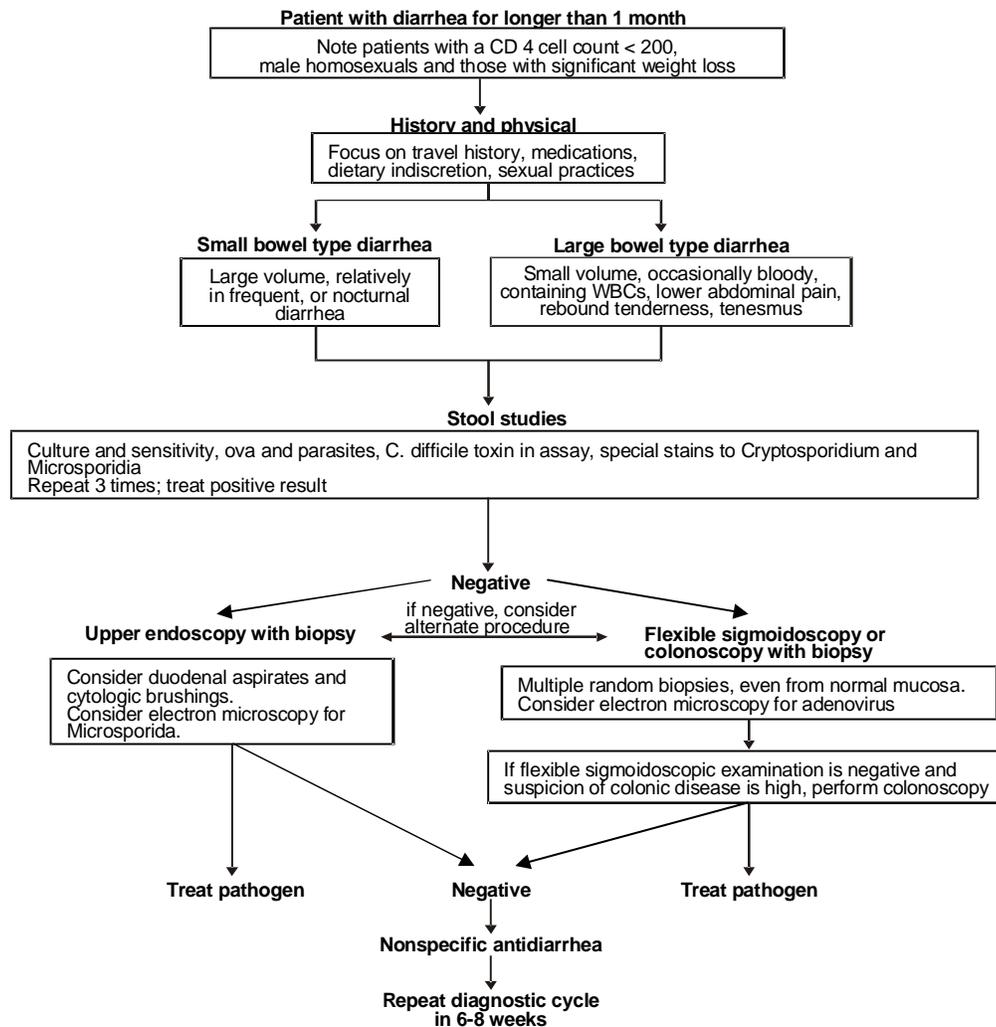
- Drugs that can induce diarrhea including the *Antiretroviral* (ARV) agents, which usually of the PI (Protease Inhibitor) agents should be evaluated. The diagnosis of diarrhea caused by such drug agents can be established at least by one of three criteria, i.e.: (1) Diarrhea occurs since 3 days following the drug administration and diarrhea may become chronic i.e. > 2 weeks if the patient unaware that the drug of PI group is the cause of diarrhea and the patient keeps consuming such drug and the chronic diarrhea occurs; (2) Diarrhea relieves after discontinuing the suspected drugs; (3) Diarrhea may become recurrent when rechallenge is performed against such drugs. The use of *oat* bran tablet, pancrelipase which is synthetic enzyme of the pancreas has been proven to be effective in conquering diarrhea related to PI drugs. Diarrhea may also be reduced by calcium, which is administered in the form of calcium carbonate by 2 x 500 mg dose given with 2 hours interval from other drug administration. Oral supplement such as glutamine (10-30 g/day) or alanyl-glutamine (until 44 g/day) can reduce diarrhea in addition to increasing the ARV drug blood level. Administration of psyllium is also effective, but it may not be administered together with other HIV treatment. Loperamide may also be used (initial dose 2-4 mg, followed by 2 mg with maximal dose of 16 mg/day). When loperamide is not effective, opium tincture may be used as an alternative (initial dose 5 drops, maximal dose 15-20 drops/day), please beware of its obstruction effect.^{10,11} Ocreotide also has been studied and it has a potential to treat refractory chronic diarrhea in HIV infection.¹²
- If no drugs are known to cause diarrhea in patients, then fecal analysis examination should be performed, including bacterial culture and parasite examination. There are no special guidelines about how many times the fecal analysis should be performed, but we suggest performing 3 times fecal examination. In patients with CD4 < 200/mm³, specific fecal examination for cryptosporidia and microsporidia should be performed. When the patient's CD4 < 100/mm³, culture of *Mycobacterium* must be conducted. If there is any fever, blood culture should also be performed. In patients with a relatively high CD4 count, the result of fecal analysis is frequently negative. This is due to: (1) The effectiveness of Highly

Active Anti Retroviral Treatment (HAART) in eradicating opportunistic agents such as protozoa infection and increased CD4 influx in lamina propria of gastrointestinal tract; (2) Since there is reduced pathogenic agents resulting from effective HAART, then the cause of chronic diarrhea may in the form of other gastrointestinal disease such as inflammatory bowel disease, irritable bowel syndrome or idiopathic steatorrhea;

(3) The toxicity effect of HAART.

When the fecal examination does not reveal any result, evaluation by endoscopy and flexible sigmoidoscopy may be performed. The selection of using upper or lower endoscopy depends on case per case. If the fecal examination reveals negative result and there is no bleeding diarrhea then the next most appropriate test is flexible sigmoidoscopy. In patients with the risk of cyto-

galovirus colitis, such as in patients with $CD4 < 100/mm^3$, mucosa biopsy is performed by flexible sigmoidoscopy. Most cases of cytomegalovirus colitis can be diagnosed by flexible sigmoidoscopy. Flexible sigmoidoscopy only can not find 39% signs of cytomegalovirus colitis. Colonoscopy should be performed when the sigmoidoscopy reveals negative result or if the suspected lesion is on the proximal of colon. In patients with $CD4 < 100/mm^3$ and the risk of infection of *Mycobacterium Avium Complex* (MAC) on small intestines, the diagnosis is established by using upper endoscopy and biopsy on duodenum. However, if the result of blood culture is positive for mycobacterium, the endoscopy and biopsy will not be necessary.^{2,6,10,11}



Remark: if fever accompanies the diarrhea. Blood culture, chest radiography and urine analysis are indicated

Figure 1. Algorithm of chronic diarrhea evaluation in HIV infection¹¹

DIARRHEA AND PATHOGEN OF GASTRO-INTESTINAL TRACT IN HIV INFECTION

Diarrhea in HIV patients may be caused by bacteria, virus or parasite infection. The most common cause of chronic diarrhea in HIV generally are *Cryptosporidium*, *Cytomegalovirus (CMV)*, *Mycobacterium Avium Complex (MAC)*, *Microsporidium*.^{10,13-15} The use of ARV itself, particularly the protease inhibitor group may also cause diarrhea; therefore, it should be considered as one of diarrhea cause in addition to the aforementioned infection agents. There are some items that should be known regarding the diarrhea that occurs in HIV patients, including diet and herbal drugs that may interact with the ARV drugs that being consumed, the water that have been drunk, and the history of journey especially to the endemic area of parasite infection.^{2,7,10,16}

Table 1. Gastrointestinal pathogens in HIV infection¹⁴

Location	Pathogen
Cavum oris, nasal cavity and proximal esophagus	Candida
	Herpes simplex
Distal esophagus and stomach ileum	Cytomegalovirus
	Cytomegalovirus
	Mycobacteria
	Giardia
	Strongyloides
Colon	Isospora
	Cryptosporidia
	Cytomegalovirus
	Salmonella
	Mycobacteria
	Cytomegalovirus
	Shigella
Amoeba	
Rectum	Gonorrhoea
	Herpes simplex

The main bacteria that cause diarrhea in HIV patients are *Salmonella* spp, *Clostridium difficile*, *Mycobacterium Avium Complex (MAC)*. In addition, *Escherichia coli*, *Pleisomonas shigelloides*, *Aeromonas*, *Shigella*, *Campylobacter* spp should also be considered. Bacteremia in HIV patients is frequently caused by *Salmonella nontyphi*, which often recurrent in 25% patients in a year. In patients with AIDS, it may cause high mortality. The treatment includes long-duration antibiotic treatment and HAART.^{10,13,14,17}

Parasites that mostly caused diarrhea in HIV

infection are *Cryptosporidium*, *Microsporidium*, *Giardia*, *Entamoeba histolytica*, *Strongyloides stercoralis*, and *Isospora belli*.^{10,14,17} *Enterovirus* is the main cause of acute diarrhea in patients with HIV. Moreover, *Cytomegalovirus*, which is almost nearly found, may cause infection as well as dysfunction in all of gastrointestinal tract. *Cytomegalovirus* is taken into account as the most common virus that cause chronic diarrhea in patients with HIV.^{10,14,18}

There have been evidences that direct HIV infection on enterocytes may cause diarrhea in patients. Forrester et al, demonstrated that in HIV, there is *HIV Trans-activating Factor Protein (Tat)* that is involved and cause a relatively severe diarrhea in patients with HIV infection without other known pathogens as the cause. HIV Tat may also cause diarrhea through direct interaction on enterocytes. Tat protein also induce the human colon mucosa to secrete ion causing diarrhea with similar mechanism as enterotoxin in bacteria. In addition, Tat protein also significantly inhibits enterocytes to proliferate. The effect of Tat increases with the increased of HIV amount in the body. Such important finding is related to the importance of HAART in suppressing HIV viral load to eliminate the symptoms of diarrhea.^{10,11}

Herpes simplex and candida may cause lesion in oral cavity and esophagus. Small intestine disorder may also caused by some types of protozoa, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*, and *Salmonella*. Colitis is frequently caused by *cytomegalovirus*. In homosexual man, colitis may be caused by *Shigella* and *E. Histolytica*. Proctitis that occurs, may be caused by *gonorrhoea*, *herpes* and *chlamydia*. There have been also evidences that direct HIV infection on enterocytes may cause diarrhea in patients. In HIV infection, chronic diarrhea is gastrointestinal disorder that commonly found. Depends on the range of laboratory examination and the characteristic of patient population, the specific cause of infection is found in 30-80% patients. Several types of organism causing chronic diarrhea have been demonstrated by various authors. The result delineates that there is a variation in frequency on several types of certain micro-organisms.^{10,11,14} The etiology of diarrhea in patients with HIV is also affected by the CD4 amount in such

Table 2. The correlation between CD4 level and pathogens cause diarrhea⁵

Causative agent	CD4 range	CD4 range	CD4 mean ± SEM	Percentage of stools containing organism
<i>E. histolytica</i>	24	26	26.0 ± 0.86	12.35 ± 55.73
<i>Cyprosporidiosis</i>	28 - 186	8	112.35 ± 55.73	49.4 ± 226
<i>Isospora</i>	32 - 106	4	66.7 ± 226	17.1
<i>Cyprosporidiosis</i>	8	4	80.95 ± 2.88	67.5 ± 2.88
<i>Candida</i>	65 - 70	4	67.5 ± 2.88	82.5 ± 2.88
<i>Helminthes</i>	80 - 85	2	155 ± 125.88	140 ± 15
<i>Helminthes</i>	2	155 - 125	140 ± 15	2.86

patient.

In three studies which were conducted separately, consisted of 154 patients with AIDS and diarrhea; cryptosporidia and cytomegalovirus are the most commonly found microorganisms, followed by *Salmonella*, *Mycobacterium avium-intracellulare* and *Entamoeba histolytica*. In small amount of cases, giardia, herpes simplex and campylobacter were found as the cause of infection. In other series of studies, 1-2% causes of infection may be due to *Shigella*, *Isospora* and *Strongyloides*. More than one-third patients with chronic diarrhea have been infected by more than one organism. The other one-third patients have unknown cause. Some authors assumed that in such patients, the cause of diarrhea is the HIV itself that attacking enterocytes in gastrointestinal tract. However, recently, there are evidences that such patients may be infected by microsporidia, i.e. small tiny intracellular sporozoa, which belongs to the genus of encephalitozoon. Such organism can only be detected by intestinal biopsy and observed through electron microscope. Thorough examination can reveal the cause of chronic diarrhea in more than one-third cases. Cryptosporidia and CMV can independently found as the most common cause of chronic diarrhea. However, both are frequently found together as the cause of chronic diarrhea.^{10,13}

CONCLUSION

Diarrhea is a common problem found in patients with HIV infection, especially in patients at advanced stages. The initial approach of chronic diarrhea with HIV is by evaluating the history of illness and the temporal correlation between diarrhea and administration of ARV, especially the protease inhibitor agents. Subsequently, it is followed by fecal analysis/examination for bacteria and pathogen protozoa. When necessary, it can be followed by endoscopy examination. The unknown cause may be resulting from HIV enteropathy or microsporidia which need the examination of intestinal mucosa biopsy and electron microscopy to confirm it. The most common cause of chronic diarrhea in HIV patients generally are *cryptosporidium*, *CMV*, *MAC*, *microsporidium*.

Etiology of diarrhea may also different based on the CD4 count of the patients; therefore, a good approach management on chronic diarrhea is necessary, especially in patients with HIV infection. The era of HAART recently also reduces the incident of chronic diarrhea in patients with HIV.

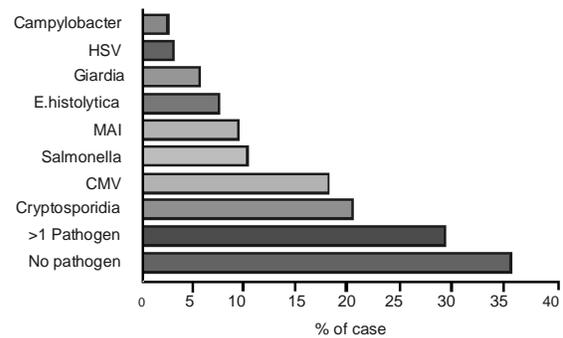


Figure 2. Intestinal infection in AIDS with diarrhea¹³

REFERENCES

- Hoffmann C, Rockstroh JK, Kamps BS. HIV medicine 2007. 15th ed. Flying Publ Paris 2007.p.33-8.
- Fauci SA, Lane SC. Human immunodeficiency virus disease: AIDS and related disorders. In: Kasper DL, Fauci SA, Longo DL, eds. Harrison's Principles of Internal Medicine. 16th ed. McGraw-Hill, New York 2005.p.1110-39.
- Djoerban Z, Djauzi S. HIV/AIDS di Indonesia. In: Sudoyo AW, Setyohadi B, Alwi I, Simadibrata M, Setiati S, eds. Buku Ajar Penyakit Dalam. 4th ed. Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI Jakarta 2006.p.1825-30.
- Call SA, Heudebert G, Saag M, Wilcox CM. The changing etiology of chronic diarrhea in HIV-infected patients with CD4 cell counts less than 200 cells/mm³. Am J Gastroenterol 2000;95(11):133-6.
- Attili VS, Gulati AK, Singh VP, et al. Diarrhea, CD4 counts and enteric infections in a hospital – based cohort of HIV-infected patients around varanasi, India. BMC Infect Dis 2006;6:39.
- Simadibrata M. Pendekatan diagnostik diare kronik. In: Sudoyo AW, Setyohadi B, Alwi I, Simadibrata M, Setiati S, eds. Buku Ajar Penyakit Dalam. 4th ed. Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI Jakarta 2006.p.357-65.
- Valori RS, Walters J, Addison GM, Hill P, et al. Guidelines for the investigation of chronic diarrhea. Gut 2003;52:1-15.
- Bartlett JG. Antibiotic guide of chronic diarrhea in AIDS. 1995 Aug [cited 2007 Jun 6]. Available from: URL:_http://www.hopkins-guide.org.
- Blumberg RS, Stenson WF, Schneider H. The immune system and gastrointestinal inflammation. In: Yamada T, Alpers DH, Laine L, et al. Yamada textbook's of Gastroenterology. 4th ed. Lippincott Williams-Wilkins, New York 2003.p.13-23.
- Forrest G, Canani RB. Gastrointestinal infections in immunocompromised hosts. Curr Opin Gastroenterol 2004;20(1):16-21.
- Dieterich DT, Poles MA, Chappell MS, et al. Gastrointestinal manifestations of HIV disease, including the peritoneum and mesentery. In: Merigan TC, Bartlett JG, Bolognesi D, eds. Textbook of AIDS medicine. 2nd ed. Baltimore Williams & Wilkins 1999.p.542-6.
- Neild PJ, Evans DF, Castillo FD, Newson R, et al. Effect of octreotide on small intestinal motility in HIV-infected patients with chronic refractory diarrhea. Dig Dis Sci 2001;46(12):2636-42.

13. Reeders JW, Yee J, Gore RM, Miller FH, Megibow AJ. Gastrointestinal infection in AIDS patient. *Eur Radiol* 2004;14:84-102.
14. Kraus CK, Rothman RE, Shahan JB. Trends in human immunodeficiency infection in the emergency Department John's Hopkins University: A 16-year Review. *SAEM Annual Meeting* 2006.p.22-30.
15. Chhin S, Harwell JJ, Bell JD, et al. Etiology of chronic diarrhea in antiretroviral naïve patients with HIV infection admitted to Norodom Sihanouk hospital Phnom Penh Cambodia. *Clin Infect Dis* 2006;43:925-32.
16. Rufo PA, Lin PW, Andrade A, Jiang L. Diarrhea-associated HIV-1 APIs potentiate muscarinic activation of Cl secretion by T84 cells via prolongation of cytosolic Ca²⁺ signaling. *Am J Physiol Cell Physiol* 2004;286:C998-C1008.
17. Mossoro C, Glaziou P, Yassibanda S, et al. Chronic diarrhea, hemorrhagic colitis, and hemolytic-uremic syndrome associated with Hep-2 adherent *Escherichia coli* in adults infected with human immunodeficiency virus in Bangui, Central African Republic. *J Clin Microbiol* 2002;40(8): 3086-8.
18. Liste MB, Natera I, Suarez JA, Pujol FH, Lifrandi DF. Enteric virus infections and diarrhea in healthy and human immunodeficiency virus-infected adult. *J Clin Microbiol* 2000;38(8):2873-7.