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Literature Review

## MANIFESTATION OF AIDS WITH DIARRHEA

Rahmat Zainuddin,<sup>1</sup> Nasronudin<sup>1,2</sup>

<sup>1</sup> Tropical and Infectious Disease Division - Department of Internal Medicine, Dr. Soetomo General Hospital - Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.

<sup>2</sup> Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia

### ABSTRACT

Infectious diseases HIV/AIDS is a global health problem. According to WHO (2000) reported that 58 million people in the world are infected with HIV, within the 22 million people died from AIDS or 7000 people die every day. HIV Infection caused decrease and disorder of humoral and cellular immunity. Intestinal mucosal normally shows a physiologic inflammation that account for intestinal mucosal integrity. Diarrhea in HIV infection due to immune deficiency can caused by pathogen and non pathogen. Acute and chronic diarrhea usually found in HIV infection patient, the latter is more frequent. HIV enteropathy cause chronic diarrhea without pathogen infection because intestinal mucous damage by HIV direct infection. Treatment is characterized as causative supportive and symptomatic treatment causal, supportive and Symptomatic. Immunonutrient is very important within management patient HIV/AIDS.

**Key words:** HIV/AIDS, diarrhea, HIV infection, immunonutrient, symptomatic

### ABSTRAK

Penyakit infeksi HIV/AIDS hingga kini merupakan masalah kesehatan dunia. Berdasarkan WHO (2000) melaporkan bahwa 58 juta jiwa di dunia terinfeksi HIV, dengan 22 juta jiwa meninggal karena AIDS atau 7000 jiwa meninggal setiap tahunnya. Infeksi HIV disebabkan penurunan dan kelainan kekebalan sel dan humoral. Mukosa usus normal menunjukkan suatu inflamasi fisiologis yang berperan dalam menjaga dan memelihara integritas dari mukosa. Diare pada infeksi HIV dikarenakan penurunan imun dapat disebabkan oleh patogen dan non patogen. Diare akut dan kronis biasanya ditemukan pada penderita HIV, akhir-akhir ini lebih sering. Enteropati HIV menyebabkan diare kronis tanpa patogen infeksius karena mukosa usus rusak akibat infeksi HIV. Pengobatan ini bertujuan untuk mengetahui penyebab, suportif dan simptomatik. Nutrisi untuk kekebalan tubuh sangat penting dalam manajemen pasien HIV/AIDS.

**Kata kunci:** HIV/AIDS, diare, Infeksi HIV, nutrisi untuk kekebalan tubuh, simptomatik

### INTRODUCTION

Infectious diseases HIV/AIDS until now is a global health problem. According to WHO (2000) reported that 58 million people in the world are infected with HIV, within the 22 million people died from AIDS or 7000 people die every day.<sup>1</sup> In the United States until January 2000 found 724,000 cases of AIDS in adults, 425 of them died.<sup>2</sup> In Indonesia (1997) recorded in the MOH are 555 cases, 423 cases of HIV and 132 AIDS cases. From a number of such cases 66 % of men, 30% women and 4% of indeterminate sex.<sup>3</sup>

Although many advances have been achieved in the field of medicine and has been implemented Secondary

prevention efforts but nonetheless progression of HIV infection to AIDS with manifestation of diarrhea are found, of which more than 50% of AIDS cases with manifestations of diarrhea.<sup>2</sup> Factors driving the emergence of diarrhea in AIDS patients is a direct effect of HIV infection and the manifestation of secondary infection. Most of the secondary infections that cause diarrhea are protozoa and cytomegalovirus infection.<sup>2</sup>

Manifestations of diarrhea in AIDS patients need to get serious attention, because it is often fatal even encourage death.<sup>4,5</sup> Based on these various circumstances discussed AIDS with manifestation of diarrhea.

## PATHOPHYSIOLOGY

HIV infection causes a decrease and disruption of the function of the immune system, especially mobile. Cellular immune system disorder characterized by a decrease in CD4 T-lymphocyte count to less than 1,000/ul. The mechanism of CD4 T-lymphocyte decline is not fully known. Some theories suggest that the direct cause of the cytopathic effect (virulence) gp 41 on the outside of the HIV virion. While indirectly occur through the process of cell apoptosis, cell destruction caused by an autoimmune response, cell maturation barriers, destruction of CD4 memory T-lymphocytes.

Decreased function of other immune system includes barriers CD4 T- lymphocyte interactions with MHC II, resulting in decreased fungal antigen presenting cells (APCs). Besides a decline in the function of macrophages and Natural Killer (NK) cells. As a result of a decrease in interferon-gamma, increased production of cytokines from T lymphocytes cells, resulting in cell proliferation and differentiation of B lymphocytes also decreased resulting in disruption humoral immune response.<sup>6,7</sup>

Disease course of HIV infection is divided into stages based on clinical circumstances and the number of CD4 T lymphocytes that includes.<sup>3,6</sup>

1. **Primary Infection;** HIV is an acute phase that lasts 6-12 weeks after HIV enters the body. CD4 T Limfositl decreased and then returned close to normal, the symptoms include fever, malaise, myalgia, arthralgia, enlarged lymph nodes and meningoencephalitis
2. **Early Immune Deficiency** (CD4 > 500/ul); Asymptomatic phase that lasts about 5 years, often no symptoms but can be Guillain-Barre syndrome symptoms, Demielinating chronic neuropathy, idiopathic thrombocytopenia, Reiter's syndrome, Bell's palsy.
3. **Intermediate Immune Deficiency** (CD4 200–500/ul); A replication phase that lasts between 5–10 years. In this phase, resulting in lysis of CD4 T-lymphocytes, are susceptible to secondary infections zooster herpes, tuberculosis, sarcoma and lymphoma nonhodgkins Kapposi's. Clinical symptoms arise usually progressive weight loss, fever without apparent cause and diarrhea.
4. **Advanced Immune Deficiency** (CD4 < 200/ul); Is the last phase (AIDS), which took place 10–13 years after infection. In this phase of severe immune deficiency causing opportunistic infections and cancers.

Intestinal immunity consists of phagocytic cells, humoral and cell mediated. Each component makes a specific contribution to the individual to an infection or inflammation of the intestine. Normal intestinal mucosa showed a physiological inflammation in the lamina propria, with the number of neutrophils, macrophages, plasma cells, and lymphocytes, which play a role in protecting and maintaining the integrity of the mucosa. Neutrophils are important in immunity, impaired neutrophil function

when the defense mechanisms in the gut also disrupted so prone to infection of the gastrointestinal tract.<sup>5</sup>

## PATHOPHYSIOLOGY DIARRHEA IN HIV INFECTION BY:

### Dirrect toxic effects of HIV

This direct toxic effect of happens due to the influence of gp 41 on the outer surface of HIV virions to the mucosa, epithelial, nervous system, causing intestinal disturbances in intestinal motility and secretion. This occurs through a process:<sup>8</sup>

- Expression of gp 41 at the membrane and budding of virus particles can cause an increase in membrane permeability, calcium influx toxic or osmotic lysis of infected cells.
- Membrane of infected CD4 T lymphocyte virus fusing with other cells that are not infected by gp 120 causes the formation of multiple multinucleated giant cells or syncytia. This process is lethal to the infected cells and uninfected.
- Viral replication can interfere with the synthesis and expression of cellular proteins that result in cell death.
- Binding of gp 120 to CD4 + T-lymphocytes induces gp 41 that have toxic effects.

This situation is known as AIDS enteropathy is due to the interaction of the HIV virus to the gastrointestinal tract. Histological picture of the patient's small bowel mucosal atrophy are lowgrade, with a decrease in the mitotic process that will lead to hyporegenerative state. Expression of p24 antigen in the intestinal mucosa will cause the inflammatory process.<sup>7</sup> This will lead to the opening of tight junctions between epithelial cells on cytokine stimulation of HIV causing diarrhea with leak flux mechanism.<sup>9</sup> The condition is often associated with chronic diarrhea mechanism, due to the morphological changes of the intestinal mucosa, causing malabsorption and decreased intestinal absorption overall.<sup>10</sup>

The reaction is caused by the HIV hipersensitifiti slow type which results in increased permeability of the intestinal mucosa, causing disruption to absorption and increased secretion of the intestinal wall which will cause inflammatory diarrhea.<sup>11</sup>

### Due to Pathogen Infection

- a. Infection from Intraluminal Intestinal  
Intestinal microflora is a normal flora is very important role in the defense in the intestine. Normal flora in the gut is important as a saprophyte which act to resist the colonization of pathogenic bacteria. Because in HIV infection is immunodeficiency, it will change to the normal flora of pathogens that would induce the secretion of chemical mediators, cytokines and inflammation in the intestinal mucosa occurs that would cause an increase in intestinal secretion and absorption disorders.

The decline in the immune system in people with HIV/AIDS led to the growth of other pathogenic bacteria in the gastrointestinal tract, such as bacterial infections, viruses, protozoa and fungi. Classically pathogens in HIV/AIDS is cryptosporidia, *Isospora belli*, *Microsporidia*, cytomegalovirus and *Mycobacterium avium - intraceluler (MAI)* which will give the manifestation in the form of chronic diarrhea.<sup>12</sup>

#### b. Secondary Infection Extraluminal

Systemic diseases can give gastrointestinal manifestations such as nausea, vomiting and diarrhea, as in pneumocistis carinii pneumonia and sepsis caused by the release of endotoxins and toxins released by microbes. Endotoxin shock is usually caused by bacterial products in sepsis can occur when there is excessive cytokines production. Production of cytokines will stimulate the release of mediators such as bradykinin, prostaglandins and leukotrine that will increase motility and increased secretion of water and electrolytes from the intestinal wall.<sup>8,10</sup>

### Etiology of Diarrhea in Patients with HIV/AIDS

HIV patients with diarrhea were not found in the intestinal pathogens found about 15–46% and the rest is caused by a pathogen invasion.<sup>11</sup>

#### Diarrhea due to Infection

All pathogens can cause diarrhea, HIV/AIDS patients. Classically pathogens in the gut in people with HIV/AIDS is *Cryptosporidia*, *Isospora belli*, and *Mycobacterium avium-Microsporidia intraceluler (MAI)*<sup>13</sup>

**Bacteria:** Pathogenic bacteria found in people with HIV/AIDS is as a opportunistic infection such as:

- *Mycobacterium avium complex (MAC)* that gives non inflammatory manifestations include diarrhea, weight loss, night sweats and hot and usually occurs in patients with CD4 + T-lymphocytes < 50 U/l. MAC bacteria are very distinctive with an overview granular nodules with a diameter of about 1-4 mm erythematous surface. Complications arising from the MAC infection is intestinal obstruction, perforation, fistula and gastrointestinal bleeding.<sup>5</sup>
- Other pathogenic bacteria that are often found include *Salmonella*, *E. coli*, *Campylobacter* and *Shigella*.<sup>11,13</sup>

**Parasit:** Intestinal opportunistic parasitic in infectious HIV patients which often cause diarrhea are *Cryptosporidi*, 20% *Microsporidia*, 4,9% *Giardia lamblia*, 2,6% *Entamoeba histolitica* and approximately 1,5% *Isoposa belli*. *Cryptosporidium* infection has secretoric diarrhea as an effect and mostly assumed that it is correlated with malabsorption. *Microsporidial* is often correlated with atrophy villus, hipper, increasing lymphocyte intraepithelial and D-xylose malabsorption.<sup>14</sup>

**Virus:** Citomegalovirus (CMV) is common and its effect on a very serious intestinal infections in people with HIV/AIDS. Symptoms of cytomegalovirus infection in gastrointestinal disease causing intermittent and persistent diarrhea and cause abdominal pain, tenesmus, heat and weight loss. Cytomegalovirus infection is more frequent cause of infection in the colon with a picture of a diffuse erythematous mucosa and submucosa that fibrils with hemorrhagic and ulcerated mucosa. Viral pathogens are also frequently found in people with HIV/AIDS, among others, the herpes simplex virus and adenovirus.<sup>5</sup>

**Fungi:** *Histoplasma capsulatum* and *Candida albicans* is a two fungal pathogen that often cause colitis in patients with HIV/AIDS. Candidiasis is a specimen that causes watery diarrhea and abdominal pain as well as the implications colonic ulcers.<sup>5</sup>

**Table 1.** Etiology agent of diarrhea in HIV infection based on the location in the intestine<sup>5</sup>

<i>Smal intestine</i>	<i>Large intestine</i>
<i>Cryptosporidia</i>	<i>Cytomegalovirus</i>
<i>Microsporidia</i>	<i>Cryptosporidia</i>
<i>Isospora belli</i>	<i>Mycobacterium avium complex</i>
<i>Mycobacterium avium complex</i>	<i>Shigella sonnei</i>
<i>Salmonella species</i>	<i>Clostridium difficile</i>
<i>Campylobacter species</i>	<i>Campylobacter jejuni</i>
<i>Giardia lamblia</i>	<i>Histoplasma capsulatum</i>
	<i>Adenovirus</i>
	<i>Herpes simplex</i>
	<i>Pneumocystis carinii</i>

#### Diarrhea caused by Non Infectious

Movement of non-infectious diarrhea in patients with HIV/AIDS need to be considered because of a neoplastic intestinal, drug reactions, lactose intolerance and pancreatic insuffisiensi secondary to pentamidine or didanosine therapy and therefore malabsorption and steatorrhea.<sup>9</sup>

### DIAGNOSIS APPROACH OF HIV WITH DIARRHEA

Approach to the diagnosis of HIV/AIDS patients with diarrhea, an important consideration is to detect movement with a degree of immune deficiency and clinical symptoms.<sup>11</sup> There is a term that is often used is the AIDS -related complex (ARC). ARC is diagnosed when there are symptoms/signs of constitutional AIDS without opportunistic infections or tumors. This concept uses for the benefit of the clinic, the alleged progression to AIDS and for prognosis.<sup>15</sup>

**Table 2.** Criteria ARC: There are 2 or more of the clinical symptoms that have lasted 3 months or more plus 2 or more laboratory abnormalities.<sup>15</sup>

Clinical Symptoms	Laboratory Abnormalities
– Fever 38° C	– Limfopeni/lekopeni
– BB decrease > 10%	– Trombositopeni
– Enlarged lymph nodes	– Anemi
– Diare intermiten/ continuou	– Ratio CD4/CD8 decrease
– Weak, Physical activity decrease	– CD4 decrease
– Night sweats	– decreasing blastogenesis, – Increasing globulin

Determination movement diarrhea Noteworthy food history, history of medicine penggunaan, travel history and symptoms along with diarrhea (nausea, vomiting, fever, other systemic symptoms) and diet (lactose) which can give clues to the cause of diarrhea. Furthermore, the determination of the degree of immune deficiency, decreased CD4 count and opportunistic infection is an indication of the decline of the immune system. Evaluation of the degree of immune deficiency useful in determining the movement of diarrhea.<sup>5,9,11</sup>

### Examination Support<sup>5,9,14,16</sup>

Microscopic examination of feces, microbiological and culture is very important in determining the movement of the symptoms of diarrhea if the infection is still a suspect. Examination is generally performed three times due to the growth of microorganisms in episodic. Examination of stool culture can detect pathogens *Campylobacter*, cytomegalovirus, adenovirus, mycobacterium avium complex and salmonella.

Acid Fast Staining Bacil (AFB) of the stool can detect pathogens mycobacterium avium complex. Antigen test to detect pathogens *Giardia* and *Cryptosporidium* are more sensitive than microscopic examination.

Endoscopic examination with biopsy be an option if you find a bloody diarrhea, tenesmus. By doing endoscopy can determine the specific location of pathogens in the gut. Diagnosis of HIV enteropathy with histopathologic examination and abnormal function of the gut with no found any pathogens or malignancy.

### MANAGEMENT

HIV patients with diarrhea therapy intended to treat HIV infection and diarrhea. Treatment of diarrhea in patients with HIV is essentially connected with a state of decreased immunity, opportunistic infections and HIV enteropathy.

Strategic treatment aimed at specific and general therapy to reduce complaints and general state of repair.<sup>8,13</sup>

### Specific Therapy

Specific therapy aimed at the treatment of HIV infection (antiretroviral therapy), provision of anti- microbial, fluid rehydration and correction of electrolyte disturbances. Provision of anti-retroviral therapy is not promptly given to patients suspected. For AIDS patients (stage III and IV disease) is recommended immediately given antiretroviral therapy irrespective of CD4 cell count or total lymphocyte count. Recommendation also be given to patients with stage II and III with number of CD4 < 200 cells/mm<sup>3</sup>.<sup>17</sup>

**Table 3.** Antiretroviral therapy<sup>17</sup>

If examination cd4 can be performed:
– Clinic stadium IV, without taking the number of CD4
– Clinic stadium I,II or III with CD4 < 200/mm <sup>3</sup>
If examination cd4 can not be performed:
– Clinic stadium IV, without taking the number of lymphocyte
– Clinic stadium II or with the number of lymphocyte < 1200/mm <sup>3</sup>

Antiretroviral drugs recommended by WHO (2002)<sup>17</sup>

Nucleosida reverse transcriptase inhibitors (NsRTI)	Non nukleoside reverse transcriptase inhibitor (NNRTI)	Protease inhibitors
Abacavir; Tablet 300 mg, Syrup 100 mg/5 ml	Efavirens; Kapsul 50 mg, 100 mg, 200 mg	Indinavir; Kapsul 100 mg, 200 mg, 333 mg, 400 mg
Didanosin; Tablet 5 mg, 100mg, 150 mg, 200 mg	Nevirapine; Tablet 200 mg, Syrup 50 mg/5 mg	Ritonavir; Kapsul 100 mg, Syrup 400 mg/5 ml
Lamivudin; Tablet 150 mg, Syrup 50 mg/5 ml		Lopinavir + ritonavir; Kapsul 133,3 mg + 33 mg, Syrup 400 mg/5 ml + 100 mg/5 ml
Stavudin; Kapsul 15 mg, 20 mg, 30 mg, 40 mg, Syrup 5 mg/5 ml		Nelfinavir; Tablet 50 mg, Powder 50 mg/g
Zidovudin ; Kapsul 100 mg, 250 mg, 300 mg		Saquinavir; Kapsul 200 mg

Therapeutic response sometimes is a tool in establishing a diagnosis of diarrhea caused by an infection. If the stool examination found no pathogenic organisms empirical therapy trial with a quinolone (ciprofloxacin) and metronidazole can be given for 1-2 weeks prior to the examination endoskopi. Standard treatment regimens for movement of infection in HIV/AIDS patients with diarrhea.<sup>14,16</sup>

Cryptosporidiosis were paromycin 500 mg every 8 hours for 14 days, azitromycin, and Letrazuril. Isosporiasis were trimethoprin – sulfamethosaxole 160/800 mg every 6 hours for 10 days, then thrice a day for 21 days, metronidazole, and pyrimethamin. Microsporidiosis was albendazole 400 mg every 12 hours for 14 days. Salmonella, shigella, enterocolitis were ciprofloxacin 500 mg every 12 hours for 14 days, cefotaxime, ceftriaxone, and chloramphenicol. Campylobacter colitis was erytromycin 500 mg every 6 hours. Mycobacterium Avium Complex was rifabutin 300 mg every days added ethambutol 400 mg every 12 hours dan claritromycin 500 mg every 12 hours. Cytomegalovirus was ganciclovir 5 mg/KgBB every 12 hours for 14 days. Candida Albicans, Histoplasma capsulatum were nystatin oral, amphotericin B, intraconazole, fluconazole used systematically in severe cases.

Lack of fluids and electrolytes cause serious problems in a patient with severe diarrhea. Monitoring immediate fluid replacement especially for severe diarrhea so that the volume of fluid lost should be measured and the amount of fluid and electrolyte replacement should be done immediately.<sup>5</sup> Oral rehydration with fluids containing glucose, Na, K, Cl and bicarbonate is effective in patients with mild dehydration. Parenteral fluid administration (Ringer's lactate) is given in the acute state of severe dehydration.<sup>12</sup>

### General Therapy

Therapy aimed at the general supportive and symptomatic treatment, nutritional support and counseling to people with HIV/AIDS. Symptomatic treatment is very important for all patients with diarrhea in the case to prevent fluid loss and improve disturbance and functional status of patients. Symptomatic therapy, among others:<sup>18</sup>

- Luminal anti diarrhea such as Bismuth subsalicylate or aluminum antacids, cholestyramine, recommended especially in mild cases
- Antimotility agents including loperamide 2–4 mg given four times a day or diphenoxylate 2 tablets given four times daily.
- Octreotide 100–500 mcg administered subcutaneous or intravenously every 8 hours, especially given the severe cases that do not respond to oral medications.

In HIV-infected patients often have impaired nutrient intake caused a decline in the body's biological functions. Immunonutrient important to consider in the management of patients with HIV/AIDS, which contains a variety of materials that can meet the needs of patients who have an infection. Immunonutrient contains the components necessary to meet basic metabolic needs are carbohydrates,

proteins, fats and also contains 3 main imunonutrient namely arginine, glutamin and fish oil that have a positive impact on the immunological function of the body. The supplement should also contain a variety of vitamins (vitamin C and vitamin E) and minerals (Mn, Cu, Se and Zn) that has the ability of anti -oxidants as well as exogenous triggers endogenous anti-oxidant potential and has anti-apoptotic effects.<sup>19,20</sup>

Nutrition given orally if the patient is still able to eat. Oral nutritional supplements should be given in the form of a convenient and easily absorbed nutrient dense. Enteral nutrition orally given if insufficient or limited by the presence of lesions in the mouth and esophagus until the patient is able to maintain sufficient oral intake. Parenteral nutrition and oral performed when enteral nutrition can not be tolerated in considerable amounts. Parenteral nutrition is given on a case by forceful vomiting and prolonged and severe diarrhea.<sup>21</sup>

### SUMMARY

HIV Infection caused decrease and disorder of humoral and cellular immunity. Intestinal mucosal normally shows a physiologic inflammation that account for intestinal mucosal integrity. Diarrhea in HIV infection due to immune deficiency can caused by pathogen and non pathogen. Acute and chronic diarrhea usually found in HIV infection patient, the latter is more frequent. HIV enteropathi cause chronic diarrhea without pathogen infection because intestinal mucous damage by HIV direct infection. Treatment is aimed to causal, supportive and symptomatic. Immunonutrient very important within management patient HIV/AIDS.

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