Original Article

# Risk Factors of Chronic Diarrhea in HIV-Infected Children

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**Abstract:**

**Background.** Chronic diarrhea increases mortality and other long-term morbidities in children. HIV-infected children are at higher risk of developing chronic diarrhea.

**Objective.** This study aimed to investigate the characteristics, prevalence, and risk factors of chronic diarrhea in HIV-infected children.

**Methods.** Data were obtained retrospectively from medical records of HIV-infected children at Dr. Cipto Mangunkusumo General Hospital (RSCM) from January 2014 until December 2016. The risk factors evaluated included age, nutritional status, dehydration status, HIV-infection phase, use of antiretroviral (ARV) drugs, and stool culture. All data that fulfilled the inclusion criteria were analyzed by bivariate followed by multivariate analysis, except for stool culture.

**Results.** The prevalence of chronic diarrhea in HIV-infected children in RSCM was 12.98%. Analysis of 132 data showed that chronic diarrhea was significantly associated with low nutritional status (p=0.037; adjusted OR=5.737) and dehydration (p=0.026; adjusted OR=6.891) among HIV-infected children.

**Conclusion.** Dehydration status and malnutrition are important risk factors for chronic diarrhea in HIV-infected children. These findings may also support that in managing HIV-infected children with diarrhea, one should first overcome dehydration and manage malnutrition to prevent the vicious circle of diarrhea – malnutrition – diarrhea.

**Keywords:** chronic diarrhea, HIV, infant, malnutrition, dehydration

## Introduction

Human Immunodeficiency Virus (HIV) infection remains one of the healthcare highlights in the current age of health. With an estimated global count of 2,100,000 newly infected with HIV, this disease causes morbidity and mortality not only in adults but also in the pediatric population.[1] In Indonesia, about 25,000 children are living with HIV.[1,2]

Children living with HIV are at a higher risk of infection and illness, including diarrhea, compared to healthy children of their age. Even in HIV-negative children, diarrhea is a prevalent disease as well as one of the leading causes of death in toddlers in developing countries, with an estimated number of annual global death of up to

800,000.[2-5] Thirty-five percent of this death is attributed to chronic diarrhea.[6] Chronic diarrhea often occurs in HIV-positive children. One study pointed out that chronic diarrhea, specific skin lesions, and failure to thrive are conditions that highly indicate the presence of HIV infection in children.[7] Other than death, chronic diarrhea causes an array of conditions, including growth and development problems as well as cognition impairment.[8-11]

## Method

This study is a cross-sectional study aimed to find out the correlation between age, nutritional status, dehydration status, HIV infection phase, antiretroviral (ARV) drug usage, and chronic diarrhea incidence in HIV-positive children. Data were obtained from medical records of pediatric patients with HIV infection at Dr. Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia from January 2014 until December 2016. Data were excluded if they did not contain all the factors included in the study (diarrhea status, age, nutritional status, dehydration status, HIV infection phase based on T-CD4$^+$ cell count, and ARV drug usage).

Data were analysed using bivariate analysis and continued with multivariate analysis of eligible factors. In addition, data on breastfeeding status in subjects with chronic diarrhea aged until 2 years and stool culture of subjects with chronic diarrhea were recorded.
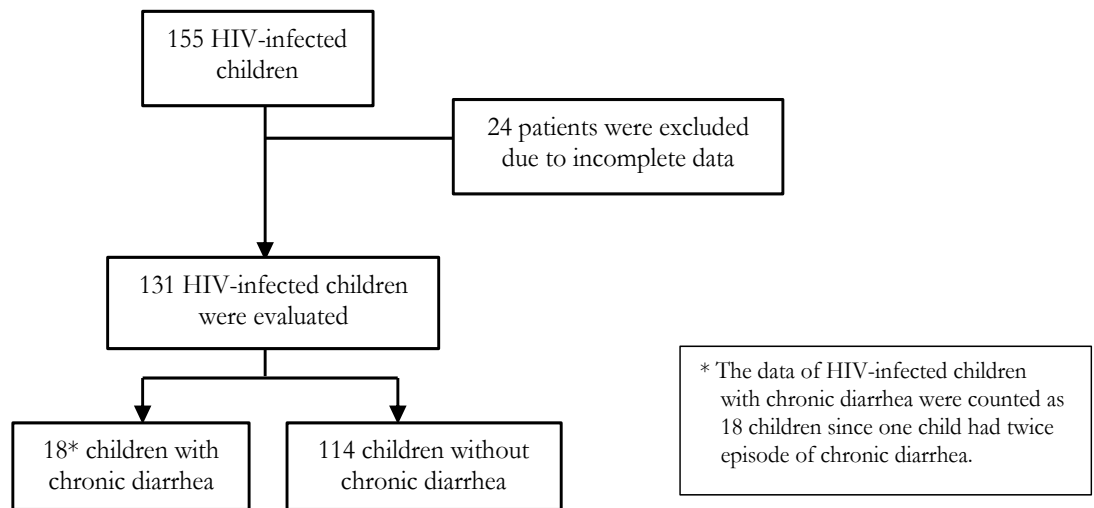


**Figure 1.** The research profile of subject participants.

Chronic diarrhea was defined as an increase in daily stool frequency (more than 3 times daily) with a change of stool consistency into watery or purely liquid stool for more than 14 days. Stool frequency depicts the stool volume. The cut-off to diagnose diarrhea was increased of more than 200 gram in stool volume. The diagnosis of diarrhea was obtained directly from the medical records made by the physician-in-

charge of the patient at admission. The subjects were divided into chronic diarrhea and no chronic diarrhea.[12] Age, ARV drug usage, and dehydration status were also retrieved from the medical records. The dehydration status was based on the clinical diagnosis made by the physician at admission and was categorized into dehydrated and not dehydrated. Age is categorized into one month to 5 years and >5 to 18 years. ARV drug usage was divided based on whether or not the subject had a regiment of ARV drugs before admission.

Nutritional status was determined using the World Health Organization Child Growth Standards graph for subjects aged one month to 2 years and using the Center for Disease Control and Prevention growth chart for subjects aged 2 to 18 years based on the subjects' weight, height, and age. The nutritional status was categorized into low and normal/high nutritional status. HIV infection phase was determined based on the T-CD4$^+$ cell count. The lower the cell count, the more advanced the infection phase. The HIV infection phase was divided into 3 groups (phase-1, phase-2, and phase-3) based on T CD4$^+$ cell count.[13]

## Results

A total of 132 data from 131 subjects were obtained (one subject had two separate incidents of chronic diarrhea). From the data, the prevalence of chronic diarrhea in HIV-positive children between 2014 and 2016 was 13%. Most cases of chronic diarrhea in HIV-positive children occurred in those aged >5 – 10 years. No single HIV-positive child with chronic diarrhea had normal/high nutritional status. Other details of the study subject characteristic are shown in **Table 1**.

**Table 1.** Characteristic of HIV children with chronic diarrhea versus without chronic diarrhea (continued).

| Variables | HIV with chronic diarrhea; n(%) | HIV without chronic diarrhea; n(%) | Total (n=131) |
|---|:---:|:---:|:---:|
| **Age** | | | |
| 1-12 months | 3(33) | 6(67) | 9 |
| >12 months – 10 years | 13(15) | 75(85) | 88 |
| >10 – 18 years | 1(3) | 33(97) | 34 |
| | | | |
| **Gender** | | | |
| Male | 9(14) | 57(86) | 66 |
| Female | 8(12) | 57(88) | 65 |
| | | | |
| **Nutritional Status** | | | |
| Low | 15(22) | 52(78) | 67 |
| Normal / high | 2(3) | 62(97) | 64 |

**Table 1.** Characteristic of HIV children with chronic diarrhea versus without chronic diarrhea (continued).

| Variables | HIV with chronic diarrhea; n(%) | HIV without chronic diarrhea; n(%) | Total (n=131) |
|---|---|---|---|
| **Dehydration Status** | | | |
| Dehydration | 4(57) | 3(43) | 7 |
| No-dehydration | 1310) | 111(90) | 124 |
| | | | |
| **ARV-drug Usage** | | | |
| Use ARV | 12(10) | 104(90) | 116 |
| No ARV | 5(33) | 10(67) | 15 |
| | | | |
| **Infection State of HIV** | | | |
| Phase-1 | 6(8) | 67(92) | 73 |
| Phase-2 | 3(15) | 17(85) | 20 |
| Phase-3 | 8(21) | 30(79) | 38 |

Notes: ARV= antiretroviral; HIV = human immunodeficiency virus.

Bivariate analysis result of 132 data obtained were shown in **Table 2**. Variables with a p-value <0.2 were eligible for multivariate analysis. Significantly correlated variables with chronic diarrhea had a final multivariate analysis (**Table 3**) p-value <0.05.

**Table 2.** Bivariate Analysis Results

| Variables | Diarrhea Status | | $p$ value |
|---|---|---|---|
| | **Chronic Diarrhea** | **No Chronic Diarrhea** | |
| **Age** | | | |
| 0 – 5 years old | 11 (26.2) | 31 (73.8) | 0.004[a]* |
| >5 – 18 years old | 7 (7.8) | 83 (92.2) | |
| **Nutritional status** | | | |
| Low | 16 (23.5) | 52 (76.5) | 0.001[a]* |
| Normal / High | 2 (3.1) | 62 (96.9) | |
| **Dehydration status** | | | |
| Dehydrated | 5 (62.5) | 3 (37.5) | 0.001[b]* |
| Not dehydrated | 13 (10.5) | 111 (89.5) | |
| **HIV infection phase** | | | |
| Phase 3 | 8 (21.1) | 30 (78.9) | |
| Phase 2 | 4 (19.0) | 17 (81.0) | 0.128[a] |
| Phase 1 | 6 (8.2) | 67 (91.8) | |
| **ARV drug usage** | | | |
| Does not use ARV drug | 5 (33.3) | 10 (66.7) | 0.034[b] |
| Uses ARV drug | 13 (11.1) | 104 (88.9) | |

Notes: HIV = human immunodeficiency virus; ARV= antiretroviral. [a]Analysed using *Pearson Chi Square Test*, [b]Analysed using *Fisher's Exact Test*. *Significant result.

Data on stool culture (**Table 4**) and breastfeeding status showed further detail of the chronic diarrhea condition. Out of the 18 data with chronic diarrhea, stool culture was available on 10 subjects. The most prevalent pathogen was *Klebsiella pneumoniae*, found on 4 cultures. Other identified pathogens were *Escherechia coli* (1 culture), *Pseudomonas aeruginosa* (1 culture), and the presence of pseudohyphae (2 culture).

**Table 3.** Multivariate analysis results

| Variables | *p* value | Adjusted OR | Confidence Interval 95% |
|---|---|---|---|
| Dehydration | 0.026* | 6.891 | 1.258-37.739 |
| Does not use ARV drugs | 0.109 | 3.282 | 0.768-14.022 |
| HIV infection phase 2 | 0.776 | 0.79 | 0.155-4.013 |
| HIV infection phase 3 | 0.767 | 1.229 | 0.315-4.797 |
| Low nutritional score | 0.037* | 5.737 | 1.108-29.698 |
| Age | 0.065 | 2.987 | 0.935-9.543 |

Notes: HIV = human immunodeficiency virus; ARV= antiretroviral. *Significant results.

**Table 4.** Positive culture in patient with chronic diarrhea

| Organisms | Number of identified organism(s) |
|---|---|
| *Klebsiela pneumoniae* | 4 |
| *Escherechia coli* | 1 |
| *Pseudomonas aeruginosa* | 1 |
| Fungi | 2 |
| None | 8 |

# Discussion

## 1. Correlation Between Dehydration Status and Diarrhea.

In this study, dehydration and nutritional status were significantly correlated with the incidence of chronic diarrhea among HIV-positive children. Dehydration is a well-known clinical condition caused by the water loss in diarrhea and is now instated the main pillars of diarrhea treatment. However, the relationship may go both ways. Dehydration observed among judo athletes by Chishaki et al. indicated that dehydration causes immunosuppression, causing changes in the IgA, IgM, and IgG ratios in the body and decreasing the phagocytic activity of neutrophils. However, the cell count is actually increased.[17] Fortes et al. studied in more detail the relationship between dehydration and immune system function in the saliva and revealed that dehydration is associated with a lower secretion rate of α-amylase and lysozyme.[18]

## 2. Correlation Between Nutritional Status and Diarrhea

Similar to dehydration, diarrhea causes suboptimal processing of ingested nutrients that ultimately leads to decreased nutritional status in the long run. A study by Palupi et al. in Yogyakarta showed similar results to this study, with low nutritional status and days of hospitalization in children with acute diarrhea having a significant positive correlation.[19] A condition of low nutritional status causes further worsening of the infectious process through alterations of various immune functions, such as the decrease in the cytotoxic activity of Natural Killer (NK) cells and neutrophils. These alterations occur as a direct effect of micronutrient deficiency, namely zinc and vitamin A.[20] It is not yet known, however, the actual level of micronutrients in these patients and which micronutrients are the exact cause for this immunodeficiency. A study in Kenya showed that the daily consumption of HIV-positive people is similar in quantity and quality to others of the same background that are HIV-negative. This study proved that the low nutritional score that happens in HIV-positive children with chronic diarrhea was more greatly attributed to the diarrhea than to the HIV infection.

## 3. Correlation Between Age, HIV Infection Phase, and ARV Usage

Age is associated with immunological maturity. The most common etiology of diarrhea varies with age group, like in infants and children under three years old who usually suffer viral diarrhea. Behavioral factors may also contribute to the infection, usually by creating opportunities for infection by oral manipulation of unclean hands. Although subjects with chronic diarrhea in this study are mostly under 10 years old, the statistical analysis was insignificant. The infection phase of HIV also correlates with immunological capability and is theoretically impaired as infection phase rises. Findings from this study contradict a study by Nsagha and colleagues in Cameroon.[21] In their study, intestinal infections in HIV-positive cases are correlated with the T $CD4^+$ cell count.[21]

The gastrointestinal system contains an abundant amount of lymphoid tissues near the mucosa as protection against the microbes in the gut.[22-26] This anatomical placement of lymphocytes further highlights the hypothesis that a decrease in the T $CD4^+$ cell would cause the body to be more susceptible to infections, especially in the intestine. Usage of ARV drugs counters the reduction in T $CD4^+$ cells, increasing immunity against infectious diarrhea. In this study, the T $CD4^+$ cell and ARV usage did not yield a significant result. The insignificant resut may be because the etiology of diarrhea is not always an infection. A decrease in T $CD4^+$ cell count may also alleviate inflammation in the intestinal mucosa caused by direct infection of the lymphoid tissue, hence explaining the unclear correlation between HIV infection phase and the incidence of chronic diarrhea.[22-26] The same logic may apply to the usage of ARV drugs, as some drugs cause diarrhea by unknown mechanisms.[15]

## Conclusion

Dehydration status and malnutrition are important risk factors for chronic diarrhea in HIV-infected children. These findings may additionally support that in dealing with HIV-infected children with diarrhea, one should overcome dehydration first and manage the malnutrition to prevent the vicious circle of diarrhea – malnutrition – diarrhea.

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