

# Management of chronic diarrhea in HIV-infected patients: current treatment options, challenges and future directions

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**Abstract:** Diarrhea is a common clinical manifestation of HIV infection regardless of whether the patients have AIDS. HIV and malnutrition tend to occur in the same populations, the underprivileged and resource-poor. Malnutrition increases severity and mortality of infection. Occurrence of chronic diarrhea in HIV-infected patients, gut status and pathogenic agents, nutritional status and the crucial role of nutrition are reviewed. Bovine colostrum-based food can be useful for managing chronic diarrhea in HIV-infected patients, enhancing both nutritional and immunological status.

**Keywords:** HIV, diarrhea, nutrition, bovine colostrum, CD4+

## Introduction

Infection with HIV imposes monumental suffering on afflicted individuals, and in the developing world in particular it places a great burden on the medical system. It is generally estimated that close to 100% of HIV-positive patients in the developing world may suffer from chronic diarrhea, as estimated on a cumulative life-time incidence, but the situation in the developed world is better, where a lower percentage of HIV-positive patients suffer from diarrhea.<sup>1</sup> It is well known that HIV destroys the immune system and renders patients susceptible to opportunistic infections. The virus also leads to enteropathy, causing a partial villous atrophy with subsequent malabsorption.<sup>2</sup>

Patients are usually diagnosed with diarrhea when three or more defecations occur per day; chronic diarrhea is diagnosed when this pattern is sustained for more than 3 months. Chronic diarrhea is not a life-threatening condition, but it can severely diminish quality of life. In conditions of poor sanitation it places a particularly heavy psychological and social burden on afflicted patients. Chronic diarrhea in HIV patients is also an AIDS-defining condition, according to World Health Organization (WHO) criteria.

## Etiological pathogenic agents

In a situation where immunodeficiency develops in HIV-infected individuals, one of the hardest-hit organs is the intestine. First, the enterocytes can undergo atrophy, as a result of the HIV virus infecting the enterocytes and damaging their function.<sup>2,3</sup> Second, as the intestine is the largest immunological organ in the body, destruction of immunocompetent cells in the intestine will cause intestinal dysfunction, which is among several symptoms observed in diarrhea.

Numerous studies have shown that diarrhea in HIV/AIDS can be caused by common pathogens, including viruses, fungi, bacteria and helminthes. What also complicates

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the situation is that, as well as infection by regular pathogens, the risk of infection by opportunistic agents increases as the patients become immunocompromised.<sup>4-7</sup> There is however no specific mix of pathogens and opportunistic agents present in HIV-associated diarrhea, but the enteric pathogens vary from patient to patient and from country to country.

One pathogen, which in immunocompromised HIV-positive individuals can cause chronic diarrhea, is *Cryptosporidium*. In immunocompetent individuals this infection is usually self-limiting, but not in HIV-positive immunocompromised individuals. Generally, no effective treatment of chronic diarrhea in HIV-positive immunocompromised individuals is available, but the mainstay of treatment is treatment with antiretroviral therapy (ART).

Numerous studies have documented the pathogens that can be found in patients with HIV-associated diarrhea.<sup>4-7</sup> The consensus seems to be that all known pathogens and intestinal opportunistic agents can cause chronic diarrhea. A diagnostic work-up is needed for each patient, if possible. The work-up can be limited to fecal cultures and microscopy, but may also include rectal and/or other intestinal biopsies.<sup>4-7</sup>

Some studies report high yields of identified causative agents while others report low figures. Diarrhea is not life-threatening, but can severely hamper daily activities and lower quality of life. Diagnostic efforts should be made to try to find the causative agent and to treat with antibiotics and other specific therapies if possible. One study suggested that in immunocompetent individuals, defined as those with a CD4+ count of  $>200/\mu\text{L}$ , the infecting agents were ordinary pathogens, while in individuals with a CD4+ count of  $<200/\mu\text{L}$ , the infecting agents were opportunistic agents.<sup>8</sup>

However, the mainstay of therapy in chronic diarrhea of HIV-positive individuals in countries where it is economically and socially feasible, is treatment with highly active ART (HAART).

The risk of chronic diarrhea in HIV-positive patients has been reduced dramatically where HAART is accessible, and the decision to introduce HAART is now taken at higher CD4+ levels. However, HAART is associated with lipodystrophy, which in turn is related to insulin resistance and its metabolic complications, such as impaired glucose tolerance, diabetes and hypertriglyceridemia.<sup>9-11</sup>

## The pivotal role of CD4+ levels

As the HIV infection progresses and the viral load increases, the CD4+ count will decrease. CD4+ lymphocytes are

T-helper cells, and are directly struck in the HIV virus attack as the HIV virus enters these through the CD4+ receptor. After entering these key cells in the immunological defense system, the HIV virus rapidly proliferates and destroys these cells. Where the CD4+ count is  $<200/\mu\text{L}$ , AIDS exists by definition.

A variety of ARTs are now available, which can decrease the viral load and increase the CD4+ count. In affluent societies HIV infection is not considered a deadly disease, but a chronic illness, which demands constant and varied antiretroviral medication to slow down virus replication, with the goal of achieving a low number of viral copies in the blood and a reciprocally high number of CD4+ cells.<sup>12,13</sup> This is however not possible in developing countries, where nutrition and sanitation are poor, which increases the risk of protracted chronic diarrhea.

Although at one predetermined CD4+ level there is an indication for treatment with HAART, different studies suggest that with proper nutritional support the chances of HAART treatment reducing disease burden increase.<sup>14</sup> Also, as HAART treatment can induce adverse effects, especially metabolic side effect, and also diarrhea, the longer the introduction of HAART is postponed the better. So postponing the introduction of HAART by introducing a nutritional treatment of a varied and healthy diet, which is rich in micronutrients, or by adding nutritional additives, for example, preparations rich in colostrum, could be very rewarding.

## The role of nutrition in hindering progression of HIV disease

There is good consensus that malnutrition has a negative impact on survival in HIV disease, even when ART is at hand. In addition, malnutrition at introduction of ART is associated with early mortality,<sup>14-18</sup> with a low body mass index as its independent predictor.<sup>19</sup>

Nutritional support can result in restored intestinal function<sup>20</sup> and weight gain in HIV-infected children.<sup>21</sup> The patients reported in both these studies were enrolled before HAART was available. An increase in CD4+ cell numbers could be observed in one of these studies,<sup>20</sup> especially if nutritional support were provided before a terminal stage of HIV infection, whereas nutritional support of children with advanced HIV infection reported by Rollins et al<sup>21</sup> resulted in sustained weight gain but not improved CD4+ count or survival.

One question that has attracted a great deal of attention is whether micronutrient supplementation can decrease

wasting in HIV disease. Wasting is probably caused by several mechanisms, where diarrheal disease caused by enteric pathogens, opportunistic infection and enterocyte destruction are among the causative factors. One study from Tanzania showed that a combination of vitamins C and E and vitamin B complex slowed weight decrease in HIV-infected women and delayed HIV progression significantly.<sup>22</sup> Another study, which was a randomized trial comparing vitamin supplementation with placebo on HIV disease progression, showed that multivitamins increased CD4+ and CD8+ counts and lowered viral load compared with placebo.<sup>23</sup> Thus, in this study multivitamins slowed progression of HIV disease. However, a Cochrane study conducted by Irlam et al found no conclusive evidence that micronutrients reduce morbidity or mortality in HIV-infected adults but the authors concluded that the WHO recommendations for micronutrient supplementations should be followed.<sup>24</sup>

However, micronutrient supplementation is just one part of good general nutrition and the overall recommendation should be that HIV-infected patients, if it is socially and economically feasible, should have a good and varied nutritional intake.

Many publications can be found on the effect of micronutrient supplements on HIV progression in both children and adults,<sup>22,23,25,26</sup> but there are few reports on the role of macronutrients for improving survival of HIV-infected individuals. However, it has been shown that HIV-positive patients with opportunistic illness have increased rates of catabolism and require greater protein intake to minimize loss of lean body mass.<sup>27</sup> An anticatabolic effect of nutritional supplements (containing 2510 kJ, complete macro- and micronutrients) combined with dietary counseling in HIV-infected subjects was reported by Berneis et al.<sup>28</sup> The diminished whole body protein catabolism resulted in a change of body composition (increased lean mass, decreased fat mass). Current evidence supporting macronutrients supplementation for malnourished HIV-infected adults has been recently reviewed by Koethe et al.<sup>29</sup> The authors suggested a range of variables for future macronutrient-based trials for malnourished HIV-infected persons in order to succeed with ART programs.

## The role of a structurally intact small intestine

As early as 1984, Kotler and associates described an HIV-associated enteropathy with structural resemblance to celiac disease.<sup>3</sup> There is thus a reduced villous height

in HIV infection and also a CD4+ mucosal lymphopenia and an increase in CD8+ lymphocytes. Further, there is an enhanced intestinal permeability, possibly leading to a greater influx of lipopolysaccharides, which are bacterial antigens from Gram-negative bacteria.<sup>30</sup> This can clearly be a factor that causes diarrheal disease and exacerbates or causes malnutrition.

## Role of bovine colostrum in treatment of HIV-associated diarrhea

A few observational studies have been published on the effect of bovine colostrum preparations in HIV-associated diarrhea.<sup>31–36</sup> In one of these a substantial therapeutic effect was reported in 25 patients, 40% of whom had a complete remission and 24% a partial remission of diarrheal disease post treatment.<sup>32</sup> In other studies, the efficacy of treatment with colostrum preparations was reported in *Cryptosporidium*-associated diarrhea in patients with AIDS.<sup>34–36</sup>

Bovine colostrum is the first milk the lactating cow gives to the suckling calf during the first days of life. Its composition is quite different from that of ruminant milk in established lactation and is characterized by its very high level of several bioactive components: immunoglobulins, growth factors, some whey proteins and proteinase inhibitors, vitamins and minerals. The biological function of colostrum is to, through its composition, provide the calf with passive immunity, support calf growth and prevent gastrointestinal infections until the calf's own immune system is fully functional.

The immune system of the newborn has been shown to be stimulated by colostrum which works to speed up the maturation of B-lymphocytes. Colostral immunoglobulins, the amount of which can be 50–250 times higher than in milk during established lactation,<sup>37</sup> may both treat and prevent viral and bacterial infections. In addition, colostrum contains lactoferrin, a protein that has been shown to transport essential iron to hematopoietic cells and prevent harmful viruses and bacteria from getting the iron they need for their growth. Bovine colostrum is also known to contain growth factors, the major forms of which are IGF-1 and TGF- $\beta$ 2, the composition of which is identical to that found in humans. They can promote mucosal recovery and gut integrity in patients with severe diarrheal illness. A study in rats showed that bovine colostrum preparation can heal the injurious effects of nonsteroidal anti-inflammatory drugs, which cause increased gastrointestinal permeability.<sup>38</sup> High amounts of Zn and Se, whose importance to the immune system is well

known, have also been reported in colostrum.<sup>39</sup> Low levels of plasma Zn and Se are associated with the deterioration of immune system and higher mortality.<sup>40,41</sup>

We have used ColoPlus® *IMCARE* (ColoPlus, Malmö, Sweden), a therapeutic food product based on bovine colostrum powder, in studies on HIV/AIDS patients suffering from diarrhea and malnutrition. The product was developed for this application. The nutritional value of ColoPlus® *IMCARE* is shown in Table 1. ColoPlus® *IMCARE* has been tested in clinical studies on HIV-positive patients in two settings in Nigeria<sup>42</sup> and Uganda.<sup>43</sup> Both studies showed that ColoPlus® *IMCARE* can alleviate diarrheas, increase body weight and induce significant increase in CD4+ levels.

ColoPlus® *IMCARE* is made and delivered in powder form and has to be mixed with water to obtain a porridge suitable for consumption. No side effects have been reported. The proposed portion size, suitable for flexibility of use and handling, is 25- or 50-g sachets.

ColoPlus® *IMCARE* consists of two parts, a bioactive part (colostrum) and a vehicle. The vehicle is composed of organic particulate matter, which is used to slow down and control the time required to empty the stomach, thus prolonging transit time of bioactives through the digestive tract, increasing contact time with the mucosal surface of the gastrointestinal tract and causing local immunological response. Survival and resistance of the bioactive parts in the gastrointestinal tract are also increased.

Colostrum powder quality is of crucial importance for the therapeutic effect of the product. Industrial processing of colostrum for ColoPlus® *IMCARE* manufacture is carried out carefully to prevent its balanced system from distortion of bioactive peptides and protein denaturation. In product formulation, a principle of “entire colostrum system” is used. All the bioactive components in colostrum act synergistically in such a way that improves the overall

effect of each individual component. Without further fractionation, some of the components that make up colostrum, such as carbohydrates, proteins and salts, can protect more sensitive components of colostrum from inactivation during the conventional processing used in the dairy industry.<sup>44</sup> The quality is determined by the IgG content, which is an established marker for liquid colostrum quality, with growth factors being positively correlated with Ig levels.<sup>44</sup>

To ensure that the effects of ColoPlus® *IMCARE* were sustained, CD4+ count, body weight, and frequency of bowel movements were measured in the two above mentioned studies, 2 and 5 weeks after termination of ColoPlus therapy. In both studies a sustained effect of ColoPlus, as measured by the above mentioned parameters, was apparent. The therapeutic effect of ColoPlus® *IMCARE* was shown to last for at least 5 weeks.

Thus, in these studies ColoPlus® *IMCARE* not only significantly increased CD4+ level but also alleviated diarrhea and sustained weight gain. Thus, this colostrum-based food product, through its bioactive content combined with micronutrients and high quality macronutrients, such as essential amino acids and carbohydrates, could improve both the immune and nutritional status in HIV-infected individuals.<sup>42,43</sup>

## Challenges and future directions

Challenges for the future are partly socioeconomic and partly medical. Socioeconomically, the overall aim for HIV-associated diarrhea should be that all disease-stricken individuals should have access to HAART. Of course, a proper medical investigation and directed therapy should be undertaken for each individual. Once this is in place, the challenge is to ensure that antiretroviral agents can act optimally. In doing so, there should be a high emphasis on good and adequate nutritional therapy. Also, we believe that special nutritional regimes such as colostrum-based therapies could have a role in this situation, especially as an adjunct to treatment of HIV-associated diarrhea.

However, the world's resources are limited, especially in the developing countries. One priority would under such circumstances is to try to postpone the need for antiretroviral agents or HAART by introducing adequate nutritional support. Colostrum-based remedies can have a crucial role in sustaining CD4+ levels and can also diminish viral load, thereby saving time until the introduction of antiretroviral agents. Adverse effects, especially metabolic, of ART,

**Table 1** Nutritional value of ColoPlus® *IMCARE*

Energy value	1650 kJ/360 kcal
Protein, g	23.0 ± 2.0
IgG, g	7.4 ± 1.2
Fat, g	2.0 ± 0.2
Carbohydrate, g	69.0 ± 2.0
Lactose, g	6.0
Sucrose, g	4.0
Ash, g	2.0 ± 0.2
Dry matter, g	96.0 ± 0.5

**Note:** values are per 100 g dry product.

including HAART, means that their introduction should be delayed as long as possible.

An ongoing trial, the CORAL study, is measuring the effect on CD4+ counts of combining hyperimmune bovine colostrum with the antiretroviral drug raltegravir.<sup>45</sup>

## Disclosure

The authors report no conflicts of interest.

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