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**ORIGINAL ARTICLE**

# ColoPlus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea

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**Abstract**

***Objective***. HIV-associated diarrhoea occurs in nearly all patients with acquired immunodeficiency syndrome (AIDS) in the developing countries. Diarrhoea is caused by the HIV-related immune dysfunction and is pivotal in the decrease of the helper T-cell (CD4+) population. Enteric pathogens in HIV-associated diarrhoea are, for example, Cryptosporidium, Amoeba and Campylobacter species. Bovine colostrum is the first milk the suckling calf receives from the cow. It is rich in immunoglobulins, growth factors, antibacterial peptides and nutrients. It supplies the calf with a passive immunity before its own active immunity is established. ColoPlus is a product based on bovine colostrum and is designed for slow passage through the gastrointestinal tract, as well as having a high nutritional value. The aim of the study was to investigate whether ColoPlus given orally can influence the severe diarrhoea associated with HIV infection. ***Material and methods***. The study was carried out at Braithwaite Memorial Specialist Hospital, Port Harcourt, Nigeria. Thirty patients with HIV-associated diarrhoea were included in the study. The patients were treated with ColoPlus for 4 weeks in an open-labelled non-randomized study, after an observational period of one week. After a post-treatment period of another two weeks, treatment with anti-HIV drugs was started, if deemed appropriate. The effects on the frequency of stool evacuations per day, on body-weight, fatigue, haemoglobin levels and CD4+ counts before (week 1) and after treatment with ColoPlus (week 7) were measured. ***Results***. There was a dramatic decrease in stool evacuations per day from $7.0 \pm 2.7$ to $1.3 \pm 0.5$ ($\pm$SD), a substantial decrease in self-estimated fatigue of 81%, an increase in body-weight of 7.3 kg per patient and an increase in CD4+ count by 125%. ***Conclusion***. ColoPlus may be an important alternative or additional treatment in HIV-associated diarrhoea.

**Key Words:** *CD4, colostrum, diarrhoea, HIV, malnutrition*

## Introduction

Diarrhoea is a common clinical manifestation of HIV infection regardless of whether or not the patients have acquired immunodeficiency syndrome (AIDS). Because of the profound immunosuppression caused by the HIV virus, and as the gastrointestinal tract is normally widely exposed to pathogens, opportunistic infections and infections with common pathogens do occur in these patients. Moreover, the HIV virus can cause a so-called HIV enteropathy, i.e. a malfunction of the enterocytes, which can result in malabsorption, which is another cause of diarrhoea [1].

The pathogens involved in HIV-associated diarrhoea include viruses, fungi, bacteria, helminths and protozoa. Often, several different pathogens and opportunistic agents which can cause diarrhoea can be isolated from each patient. Among the most common enteric pathogens are Cryptosporidium, Microsporidia, Entamoeba histolytica, Clostridium difficile, Campylobacter, Salmonella and Shigella.

Colostrum is the milk the lactating cow gives to the suckling calf during its first days of life. This first milk is rich in immunoglobulins, growth factors and antimicrobial factors and it is also abundant with

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nutrients. The biological function is that the contents in colostrum should support the growth of the calf and prevent gastrointestinal infections until the calf has managed to synthesize its own active immune defence system.

The immune system of the newborn is shown to be stimulated by colostrum by speeding up the maturation of B-lymphocytes. Furthermore, colostrum contains immunoglobulins, which may provide a defence in both the treatment and prevention of viral and bacterial infections. In addition, colostrum harbours lactoferrin, a protein that has been shown to transport essential iron to haematopoietic cells and to prevent harmful viruses and bacteria from getting the iron they need for their growth. It is also known that bovine colostrum contains growth factors, the major forms of which, IGF-1 and TGF-$\beta_2$, are identical in composition to the human forms. They can promote mucosal recovery and gut integrity in patients with severe diarrhoeal illness [2].

A few observational studies have been published with the aim of diminishing diarrhoea in the HIV/AIDS situation using bovine colostrum preparations [3,4]. In one of these studies a substantial therapeutic effect was reported in 25 patients, 40% of whom had a complete and 24% a partial remission of diarrhoea [3]. In other studies the efficacy of treatment with colostrum is reported in Cryptosporidium-associated diarrhoea in patents with AIDS [5–7].

The primary objective of this study was to investigate whether ColoPlus, a bovine colostrum-based food product (ColoPlus AB, Malmö, Sweden) can alleviate the severe diarrhoea occurring in HIV-positive patients with or without AIDS.

## Material and methods

### *Patient study group*

Those taking part in this study were known HIV-positive patients, 18 years of age or older, with or without AIDS, and visiting the HIV clinic at Braithwaite Memorial Specialist Hospital, Port Harcourt, Nigeria. This hospital is one of the largest in Port Harcourt with a primary enrolment area of around one million people. HIV infection is prevalent in the Port Harcourt area, with an estimated HIV infection rate of 6.6% of the population. The most common infection is HIV-1, but some of our patients were also infected with HIV-2 virus. One of us (S.C.) is in charge of the HIV/AIDS programme in Port Harcourt, Rivers State, Nigeria.

Thirty adult consecutive patients with HIV-associated diarrhoea were included in the study (15 M, 15 F, aged between 20 and 56 years). The inclusion criterion was a stool frequency of four or more evacuations per 24 h for 5 days or more. All patients gave their informed consent.

The study was approved by the ethics committee at Lund University, Lund, Sweden and also by the local ethics committee at Braithwaite Memorial Specialist Hospital, Port Harcourt, Nigeria.

### *The test product*

The test product, ColoPlus, is a bovine colostrum product in porridge form developed by ColoPlus AB in collaboration with Arla Innovation in Stockholm, Sweden and currently pending a patent. Production is carried out in accordance with the regulations of the Swedish National Board of Food Administration.

The active part of the product is collected and processed from bovine colostrum in such a way that bioactive substances such as immunoglobulins and growth factors are preserved [8]. The active test substance is then added to a vehicle, which is formed of dry rice flakes, with the addition of banana flakes and sugar to give a pleasant taste. ColoPlus is in dry-powder form particles with a diameter of 0.3–7 mm. The particle size is chosen to allow a slower intestinal transport time than for milk, in order to obtain optimal exposure by active components.

The starch-containing vehicle swells after it is mixed with water, and this protects the active substances in the bowel and contributes to increasing the transit time through the gastrointestinal tract.

The composition of the ingredients of ColoPlus is 32% colostrum powder, 30% rice flakes, 14% banana flakes, 20% maltodextrin and 4% sugar. The nutritive value of ColoPlus is summarized in Table I.

### *Study design*

The study was an open, non-randomized, observational study. No previous study with ColoPlus has been done, but we estimated that 30 would be an appropriate number of patients and that the patients could act as their own controls.

ColoPlus is packed in portions of 50 g. Each portion contains 3–4 g immunoglobulin and is mixed by the patient with 100 ml lukewarm water ($<60^{\circ}$C) just before intake. ColoPlus, which in this form has the characteristics of porridge, will be eaten as the first and last meal of the day. During the first

Table I. Nutritive value of ColoPlus. Declaration of contents.

| | Per 100 g of the dry product ColoPlus | Per one portion, 50 g |
|---|---|---|
| Energy value | 1650 kJ/350 kcal | 825 kJ/175 kcal |
| Proteins, g | 23.0±2.0 | 11.5±1.0 |
| Thereof IgG, g | 7.4±1.2 | 3.7±0.6 |
| Fat | 2.0±0.2 | 1.0±0.1 |
| Carbohydrates, g | 69.0±2.0 | 34.5±1.0 |
| Thereof lactose, g | 6.0 | 3.0±0.5 |
| Thereof sucrose, g | 4.0 | 2.0±0.4 |
| Ash, g | 2.0±0.2 | 1.0±0.2 |
| Dry matter, g | 96.0±0.5 | 48±0.3 |

week, which is an observational week, no treatment was given. During weeks 2 to 5 the patient received an addition of ColoPlus. The patients were then observed for another 2 weeks (Table II), after which antiretroviral treatment was started, if deemed appropriate. During the study, compliance with regard to consumption of ColoPlus was checked regularly and compliance was found to be almost 100%.

*Measurements*

At the start of the study, stool microscopy was done and blood samples taken for CD4+ tests. In weeks 1–7 the following parameters were studied and documented: frequency of stools per 24 h, recorded in diary cards; haemoglobin at the end of weeks 1, 5 and 7; S-albumin at the end of weeks 1, 5 and 7; body-weight at the end of weeks 1, 5 and 7; fatigue according to a self-estimated visual analogue scale (VAS) at the end of weeks 1, 5 and 7; and CD4+ count, week 1 and 7.

Haemoglobin and albumin levels were measured at the Department of Chemical Pathology, Braithwaite Memorial Hospital using standard procedures, as was stool microscopy. The self-assessing VAS consisted of a line with a scale from 0 to 10, where 0 denoted no fatigue and 10 the worst fatigue imaginable. During the visit to the hospital, the patient marked with a cross the line that she/he thought to be appropriate. WHO-recommended kits were used for determination of HIV-1 and HIV-2 infection. CD4+ count was done using the Dynal beads manual method.

Table II. Flow chart.

| No treatment \| | No treatment +ColoPlus | \| No treatment | |
|---|---|---|---|
| 0 | 2 | 5 | 7 weeks |

*Statistics*

Comparisons of values before and after treatment with ColoPlus were made with Student's *t*-test.

## Results

All 30 patients were infected with HIV-1 virus and 7 also had a concomitant HIV-2 infection. The mean CD4+ count at the beginning of the study was 153±62 cells/μl. Twenty-one patients had a CD4+ count of less than 200 cells/μl, and were therefore defined as having AIDS. At the start of the study, stool microscopy showed the following pathogens: Cryptosporidium oocysts, yeast cells, *Entamoeba histolytica* cysts, Ascaris ova, Hookworm ova, Trichuris and Strongyloides. Cryptosporidium ova were particularly common and 20 patients were observed to be infected with Cryptosporidium, while in 12 patients cysts of *E. histolytica* were observed. In four patients no pathogen was identified at stool microscopy. In this study no stool cultures and no post-treatment analysis of stool microscopy were carried out.

The mean number of bowel evacuations per day at week 1 was 7.0±2.7 (±SD) decreasing to 1.6±0.9 (±SD) at week 5, which was the last of the four weeks of treatment with ColoPlus. This effect lasted for the next two weeks, and at week 7 the mean number of evacuations per day was 1.3±0.5 (±SD) (Table III).

As secondary end-points, self-reported fatigue, body-weight, haemoglobin, serum albumin and CD4+ counts were measured. The self-reported fatigue decreased dramatically during the course of the study. At week 1 it was reported to be 8.76±1.0 (±SD) and at weeks 5 and 7 the corresponding figures were 3.23±1.5 (±SD) and 1.7±1.2 (±SD), respectively. Comparing week 7 with week 1, there was thus a decrease in fatigue by 81% (Table III).

The weight of the patients ranged between 17.4 kg and 58 kg. There was an increase in body-weight of 5.5±2.3 (±SD) kg and 7.3±2.2 (±SD) kg at week 5 and week 7, respectively, as compared with week 1. Furthermore, a concomitant increase occurred in haemoglobin and serum albumin levels of 26.8±9.7 g/l (±SD) and 10.4±4.1 g/l (±SD), respectively, in comparison with measurements done at week 7 and those done at week 1 (Table III).

An increase occurred in absolute CD4+ counts in all patients and at the end of the study(week 7), the mean count for CD4+ cells was 310±106 (±SD) cells/μl, which corresponds to an increase of 125±75% (±SD) ($p < 0.01$) (Table III). In 21 patients, who at the beginning of the study had a CD4+ count of less than 200 cells/μl, all but 3 were

Table III. Effect of ColoPlus on HIV-associated diarrhoea.

| | Week 1 | Week 5 | Week 7 | $p$-value |
|---|---|---|---|---|
| Evacuations[#] | 7.0±2.7 | 1.6±0.9 | 1.3±0.5 | <0.01 |
| CD4+ count (cells/l) | 153±62 | Not done | 310±106[¶] | |
| Body-weight, kg | 48±10 | +5.5±2.3[*] | +7.3±2.2[*] | <0.01 |
| Fatigue units | 8.76±1.0 | 3.23±1.54 | 1.7±1.17 | <0.01 |
| Haemoglobin g/l | 85.2±13.8 | +19.4±7.2[*] | +26.8±9.7[*] | <0.01 |
| Albumin g/l | 33.0±4.4 | + 7.9±3.3[*] | +10.4±4.1[*] | <0.01 |

The $p$-values refer to values at weeks 5 and 7 each compared to week 1. All values are expressed as ±SD.
[¶]Increase by 125±75% compared to week 1, $p < 0.01$.
[*]Increase in kg or g/l at weeks 5 or 7, compared to individual baseline values at week 1.

registered as having an increase to a cell count of more than 200, which by definition is no longer AIDS. The three patients who still had cell counts of less than 200 cells/μl had, however, a 120, 110 and 94% increase in CD4+ count.

No side effects of the treatment with colostrum in the form of ColoPlus were reported.

## Discussion

This open-labelled observational study shows that bovine colostrum in the form of ColoPlus can be a treatment alternative in HIV-associated diarrhoea. The effect of ColoPlus was prompt, dramatically reducing the number of evacuations of stools per day. Also, an increase in haemoglobin and albumin did occur, the patients' fatigue was alleviated and their body-weight increased. Moreover, there was a rise in the CD4+ count.

The patients are thus getting rid of their diarrhoea and are also experiencing a remarkable improvement in well-being. At this stage one can merely speculate on what impact the colostric immunoglobulins and peptides have and what impact the nutritional support has on the positive development which the patients experienced. However, on calculation, a mere 350 kcal was given daily as extra calories in the form of ColoPlus to each patient. This extra caloric supplement is beneficial, but could hardly on its own explain the overall positive effect of ColoPlus.

Diarrhoea is a common problem in HIV-positive patients with or without AIDS. In this study, as in other studies, infection with Cryptosporidium was common. In healthy, non-immunocompromised individuals, this protozoon is readily cleared and does not give chronic symptoms in the form of diarrhoea. The situation is the opposite in HIV-infected patients, where debilitating diarrhoea often occurs [9]. Cryptosporidiosis readily infects cows and therefore one expects to find immunoglobulins in colostrum, which are specifically directed against Cryptosporidium. Colostrum, which is hyperimmune, has also been produced by immunizing cows with Cryptosporidium extracts [6,7]. The immunoglobulins in native bovine colostrum have been shown to be resistant to proteolysis, possibly reflecting that colostrum contains trypsin inhibitors. This should thus apply to ColoPlus as well, although this has not been tested *in vivo*.

One astounding feature of this study was that we saw a dramatic increase in the CD4+ count. The decrease in CD4+ cell number is pivotal in establishing an immunodeficiency situation in HIV-positive patients with or without AIDS. A reasonable hypothesis is that the absence of gastrointestinal infection and diarrhoea and the improvement in metabolic and nutritional status, where instead of being catabolic the patient is anabolic, serve to increase the number of CD4+ cells.

In this case, however, we cannot rule out a direct effect of bioactivities of ColoPlus deriving from colostrum on viral replication, as in this study viral load was not measured.

The results of this observational study indicate that ColoPlus is a safe, effective supplement in the management of patients with HIV-associated diarrhoea. It is a food product, not a drug, and can be classified as functional food. The rationale for using ColoPlus in an immunodeficiency situation is that, in nature, colostrum is given in a situation where the calf by definition is immunodeficient, before its own active immunity system is established.

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