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Randomized control trials

Effectiveness of nutritional treatment and synbiotic use on gastrointestinal symptoms reduction in HIV-infected patients: Randomized clinical trial

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SUMMARY

Background & aims: Gastrointestinal symptoms are among the most frequent reported complaints by people living with HIV and AIDS (PLWHA). Treatments that aim to attenuate these symptoms are important to avoid low adherence to antiretroviral therapy and to improve the quality of life. This study aimed to evaluate the effectiveness of nutritional treatment and synbiotic use in PLWHA on reducing gastrointestinal symptoms.

Methods: A randomized clinical trial nested to an outpatient cohort was conducted to evaluate the effectiveness of two treatments for gastrointestinal symptoms reduction in adult patients with antiretroviral therapy presenting at least one gastrointestinal symptom: 1) nutritional treatment + placebo (6 g maltodextrin) and 2) nutritional treatment + synbiotic (*Lactobacillus* and *Bifidobacterium* strains + 6 g fructooligosaccharides). Placebo and synbiotic were consumed twice a day during six months. The primary outcome variable was percentage reduction in the incidence of diarrhea, and secondary outcomes the decrease in the incidence of nausea and/or vomiting, dyspepsia, heartburn, constipation, flatulence, and the presence of three or more gastrointestinal symptoms.

Results: Out of 283 patients evaluated for eligibility, 64 met inclusion criteria to enter in this study with 1:1 allocation ratio. Both analyzed groups were homogeneous regarding sociodemographic, clinical and lifestyle variables at baseline. In the intergroup analysis, no difference was found between groups except for heartburn, which had a higher reduction in the placebo group (0.01). Regarding the intragroup analysis, in the placebo group a significant decrease in diarrhea ($p = 0.02$) and heartburn ($p < 0.01$) were observed while there was a significant reduction for nausea e/or vomit ($p = 0.01$), dyspepsia ($p = 0.10$), diarrhea ($p = 0.01$) and constipation ($p = 0.08$) in the synbiotic group.

Conclusions: Diarrhea decreased in both groups, but no statistical difference between treatments was observed. The use of synbiotic appeared to reduce a greater number of symptoms although there were no statistical differences in the intergroup analysis.

This clinical trial was registered at ClinicalTrials.gov (NCT02180035).

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1. Introduction

The gastrointestinal tract is affected by HIV-infection. The intestinal immune system is the primary target of the virus [1]. HIV-infection exerts an adverse impact on the gastrointestinal system, affecting its structure and function, favoring the disease progression through bacterial translocation and generalized immune system activation [2]. Progressive loss of TCD4+ cells leads to gastrointestinal enteropathy characterized by epithelial degeneration, impairment of intestinal microvilli, and inflammation, causing discomfort, diarrhea, abdominal distention and nutritional deficiencies [3].

The intestinal tract is one of the most affected sites by the HIV-infection [4]. Before antiretroviral treatment (ART), the presence of gastrointestinal symptoms was strongly associated with the occurrence of opportunistic diseases. With the depletion of defense cells in the organism owing to the viral load increase, the HIV-infected individual becomes vulnerable to opportunistic infections caused by various pathogens, leading mostly to diarrhea [5,6].

Despite the improvement in immune function with ART use [7], adverse effects as gastrointestinal intolerance symptoms like diarrhea and nausea can occur, constituting an important factor in treatment discontinuation and poor medication adherence [8,9]. Nevertheless, the etiology of gastrointestinal symptoms in people living with HIV/AIDS (PLWHA), particularly diarrhea, may involve both factors related to ART as the HIV-infection itself [9].

Probiotics, prebiotics, and synbiotics have nutritional functions, metabolic and physiologic effects that are beneficial to health. In PLWHA, probiotics, prebiotics, and synbiotics have shown positive effects in the gut physiology, intestinal barrier integrity and improvement in the immune function, and they can be recommended as adjuvant therapy in these patients' treatment [10–12]. The use of probiotics can bring benefits on the incidence of gastrointestinal symptoms [13], while prebiotics plays a significant role in the intestinal flora, modulating and improving its composition [14].

In an extensive literature search, the use of synbiotic in HIV-infected adult patients was identified only in two studies that investigated its effect on function and integrity of gastrointestinal mucosa [10] and bacterial translocation [11]. Studies evaluating the effect of nutritional treatment and synbiotic use on gastrointestinal symptoms in PLWHA with or without ART were not found. This study assessed the effect of synbiotic supplementation combined with nutritional treatment in PLWHA on ART in reducing gastrointestinal symptoms: diarrhea, nausea and/or vomit, dyspepsia, heartburn, constipation, and flatulence, considering the assumption of the coadministration of probiotic and prebiotic potentiating action in the treatment of gastrointestinal disorders.

2. Materials and methods

This research is a double-blind randomized clinical trial nested to a larger research project called PRECOR, conducted at the Outpatient Clinic of Infectious and Parasitic Diseases (OCIPD) from Hospital das Clinicas, Federal University of Goias, Brazil. The OCIPD is one of the specialized care centers for people living with HIV/AIDS, the second Goias State's outpatient clinic with the greater flux of PLWHA. The Hospital das Clinicas of Federal University of Goias Ethics Committee approved this clinical trial, named PRECOR-NUT (protocol number 163/2009). All patients who agreed to participate signed an informed consent.

All patients receiving routine health care at OCIPD between March 2010 and July 2011 were invited to participate in PRECOR study. Adult patients in ART for at least 30 days were referred to a nutrition consultation and asked to participate in PRECOR-NUT, totalizing 176 patients. Inclusion criteria for this study was incidence of at least one gastrointestinal symptom among diarrhea, nausea and/or vomit, dyspepsia, heartburn, constipation and flatulence at the initial evaluation by the nutritionist. Pregnant and lactating women and patients with an opportunistic disease diagnosed in less than two months or more with no clinical resolution during the time of the recruitment period were excluded from the study sample. The flow diagram of patients' recruitment, entry and follow-up is shown in Fig. 1. The average interval between baseline and end of follow-up was 30 weeks.

The research coordinator generated the randomization sequence after signature of the consent form. Each patient received a random number used for simple allocation in three groups at 2:1:1 ratio. In this study, only the latter two groups were evaluated: 1) nutritional treatment + placebo and 2) nutritional treatment + synbiotic. The patients and health care professionals involved in the research were unaware of which group receives placebo or synbiotic. Synbiotic and placebo sachets were monthly distributed to the participants after the nutrition consultation. The sachets were identical, differentiating only by a serial number printed on the side of the package to maintain the blinding of the study.

The placebo group received sachets with 6 g of maltodextrin. The synbiotic group received 6 g of synbiotic containing fructooligosaccharides, *Lactobacillus paracasei* (LPC-37), *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (NCFM) *e Bifidobacterium lactis* (HN019) at a concentration of 10^6–10^9 CFU per strain (LACTOFOS©). Both groups were instructed to consume two sachets/day, one by morning and other before sleep, diluted in 100 ml of room temperature water.

A company provided synbiotic and placebo in sponsorship character according to pre-established ethical principles. This company has the product registration and follows strict development criteria according to the Brazilian National Agency of Sanitary Vigilance recommendations.

Nutritional counseling for healthy eating, individual counseling for any pre-existing medical condition such as diabetes, hypertension or dyslipidemias and for the presence of gastrointestinal symptoms composed the nutritional treatment applied to both groups. Additionally, a personalized eating plan was calculated in agreement with nutrient requirements, clinical and socioeconomic conditions. The nutritional counseling was based on the Brazilian Clinical Manual in Assistance to Adults Infected with HIV [15] and the Dietary Guidelines for the Brazilian Population [16].

The research team was previously trained for nutritional treatment's effectuation and implantation in agreement with the research protocol in order to standardize all executed procedures.

The primary outcome of this study was the intergroup percentage reduction in the incidence of diarrhea between baseline and the end of follow-up. Secondary outcomes were the intergroup percentage reduction in the incidence of other gastrointestinal symptoms (nausea and/or vomiting, dyspepsia, heartburn, constipation, flatulence, and the presence of three or more gastrointestinal symptoms).

The sample size was determined considering expected success rate of 5% for the standard treatment and 30% for the synbiotic treatment with 10% alpha and 80% power, resulting in 25.5 patients in each group [17]. Another calculation was performed considering the same parameters above with a 5% alpha, resulting in 32 patients in each arm of the study [17]. The choice of an alpha of 10% was due to the intervention's characteristics, which has low cost and has a small probability of adverse effects. In such cases, a weighing between statistical significance and clinical relevance is taken into account.

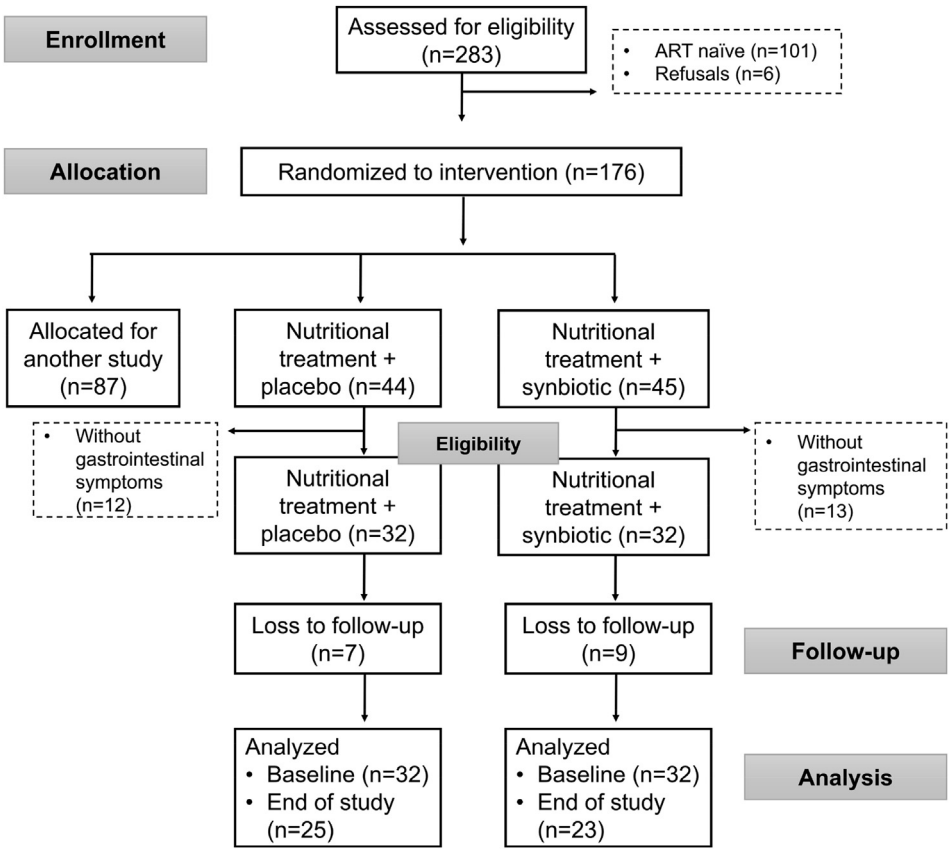

Fig. 1. Flow diagram of enrollment, allocation, follow-up and analysis of study participants.

Intention-to-treat analysis was performed. Pearson's Chi-Squared test or Fisher's Exact test were employed to test homogeneity between groups at baseline, when applicable. Intergroup analysis for assessment of percentage differences for each gastrointestinal symptoms at the end of follow-up was performed using Pearson's Chi-Squared test. McNemar's test was used to compare the intragroup reduction in gastrointestinal symptoms. The level of statistical significance was set at $p < 0.10$. All statistical analysis was conducted in Stata 12.

3. Results

Out of 176 eligible patients, 87 were allocated to another study; 44 to the placebo group; and 45 to the synbiotic group. To achieve the aims and inclusion criteria of the present study 32 patients were included in each group. Those who presented no gastrointestinal symptoms at baseline were not enrolled in this study. Sixteen patients drop out the study, resulting in 25% of loss to follow-up. There were not losses of follow-up due to adverse treatment effects (Fig. 1).

In the analysis of homogeneity between groups, statistically significant differences for the investigated variables were not observed, confirming the randomization efficiency (Table 1).

In the intergroup analysis at the end of follow-up, only heartburn was statistically different between groups ($p = 0.01$). Greater reduction in heartburn was observed in the placebo group (Table 2).

Diarrhea and heartburn were significantly attenuated in placebo group, with a percentage reduction of 52.8% ($p < 0.01$) and 14.8% ($p = 0.02$) compared to baseline, respectively (Table 3).

Synbiotic use concomitant to the healthy eating plan showed significant reduction in diarrhea (21.8%; $p = 0.01$), nausea and/or vomit (28.8%; $p = 0.01$), constipation (13.2%; $p = 0.08$), and dyspepsia (24.5%; $p = 0.10$) (Table 4).

4. Discussion

Diarrhea was the only symptom that presented a statistically significant reduction in both groups in the intragroup analysis, but this decrease was not statistically different between groups. Except for heartburn, the significant statistical difference has not been observed at intergroup analysis. The present study shows that the nutritional treatment with or without synbiotic may have beneficial effects on reducing gastrointestinal symptoms in PLWHA. Synbiotic administration on PLWHA, so far little investigated, is a promising treatment proposal as an adjuvant for ART-related gastrointestinal disorders in PLWHA.

Regarding secondary outcomes, heartburn was significantly reduced only in the group treated with placebo. In the synbiotic group, there was a decrease in dyspepsia and constipation in the established statistical significance threshold, which was not observed in placebo group. Adverse effects that may cause discontinuation of treatment with synbiotic were not observed.

The use of probiotics in different research contexts was associated with a reduction in diarrhea duration and increased stool consistency, although its efficacy is not completely elucidated [18–20]. In people living with HIV/AIDS, studies assessing probiotic supplementation report effects on immune system, reduction in HIV-infection progression and reestablishment of intestinal health [21–23]. Effects of probiotics in PLWHA was observed in adult

Table 1
Sociodemographic and clinical characteristics at baseline of HIV-infected patients on ART by treatment group. Brazil, 2011.

	Total n (%)	Placebo n = 32 n (%)	Synbiotic n = 32 n (%)
Sex			
Male	44 (68.8)	22 (50.0)	22 (50.0)
Female	20 (31.2)	10 (50.0)	10 (50.0)
Age			
19–29 years	9 (14.1)	4 (44.4)	5 (55.6)
30–39 years	18 (28.1)	8 (44.4)	10 (55.6)
40–49 years	25 (39.1)	13 (52.0)	12 (48.0)
>50 years	12 (18.8)	7 (58.3)	5 (41.7)
Marital status			
Single	32 (50.0)	15 (46.9)	17 (53.1)
Married	19 (29.7)	11 (57.9)	8 (42.1)
Widowed/Divorced	13 (20.3)	6 (46.1)	7 (53.9)
Personal income (in tertiles)			
1st tertile	25 (39.1)	14 (56.0)	11 (44.0)
2nd tertile	20 (31.2)	8 (40.0)	12 (60.0)
3rd tertile	19 (29.7)	10 (52.6)	9 (47.4)
Years of schooling			
Up to 4	12 (18.8)	7 (58.3)	5 (41.7)
5 to 8	12 (18.8)	6 (50.0)	6 (50.0)
9 to 11	23 (35.9)	9 (39.1)	14 (60.9)
12 years or more	17 (26.6)	10 (58.8)	7 (41.2)
Time of ART use			
< 1 year	10 (17.2)	5 (50.0)	5 (50.0)
1–3 years	10 (34.5)	8 (40.0)	12 (60.0)
> 3 years	28 (48.3)	14 (50.0)	14 (50.0)
NNRTI use			
No	13 (20.6)	10 (76.9)	3 (23.1)
Yes	50 (79.4)	22 (44.0)	28 (56.0)
PI use			
No	47 (74.6)	22 (46.8)	25 (53.2)
Yes	16 (25.4)	10 (62.5)	6 (37.5)
TCD4 + lymphocyte count			
<200 cells/mm^3	2 (3.2)	0 (0.0)	2 (100.0)
200–349 cells/mm^3	11 (17.7)	4 (36.4)	7 (63.6)
350–499 cells/mm^3	15 (24.2)	11 (73.3)	4 (26.7)
≥500 cells/mm^3	34 (54.8)	17 (50.0)	17 (50.0)
Viral load			
<50 copies/ml	53 (85.5)	30 (56.6)	23 (43.4)
≥50 copies/ml	9 (14.5)	2 (2.2)	7 (77.8)
Smoking status			
No	29 (45.3)	15 (51.7)	14 (48.3)
Yes	18 (28.1)	8 (44.4)	10 (55.6)
Former smoker	17 (26.6)	9 (52.9)	8 (47.1)

ART: antiretroviral therapy. NNRTI: non-nucleoside reverse transcriptase inhibitor. PI: protease inhibitor.

women in Nigeria with supplemented yogurt containing *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 during 15 days, evidencing improvement in diarrhea, flatulence, and nausea compared to placebo group [24]. These results are similar to our study, in which synbiotic has *L. rhamnosus* strain. In addition, we also observed a significant reduction in vomit, which was not investigated in the other study [24]. A study with *L. rhamnosus Fiti* supplemented yogurt also found positive results regarding diarrhea improvement in PLWHA on ART [23]. Other studies evaluating the probiotic effect on diarrhea in PLWHA did not found significant results compared with the control group [22,25].

An increase in flatulence incidence was observed after treatment with synbiotic in our study, although not statistically significant. This increase in flatulence may be related to the prebiotic compound of the synbiotic supplement, fructooligosaccharide (FOS), once this symptom is a reported side effect seen in other studies, although prebiotics are usually well tolerated [26].

A study in Brazil investigated the synbiotic use with the same composition and dosage and observed an improvement in chronic constipation in women with 30 days of supplementation, without influencing abdominal distension and flatulence [27]. In our study, a significant reduction in constipation was observed in the group treated with synbiotic. This effect can be due to the increasing fiber intake by nutritional treatment in conjunction with synbiotic use, either by the FOS or the recommendation for consuming fruits and vegetables.

Given the nature of the intervention, which is easy to perform, affordable, does not cause side effects and does not put the individual on any risk when compared to a drug intervention is essential to reflect on the clinical significance of the findings. Although statistical significance is not observed in some occasions in the present study, the changes in the incidence of gastrointestinal disorders implies substantial benefit for HIV/AIDS patients. This symptoms improvement bring greater welfare and quality of life to HIV-infected patients and may directly imply in better adherence to the pharmacological treatment, given that gastrointestinal disorders are factors that hamper maintenance of ART use, mainly in its first year of therapy [8,9].

The choice for an alpha of 0.10 could be addressed as a limitation of this study. However, although not very usual for increasing type I error probability, we opted for this approach by considering the characteristics of the study intervention, as mentioned above. Additionally, the sample size was calculated with an alpha of 0.05, and it was also sufficient to detect differences in the outcome variable.

In the context of HIV-infected patients, promotion of adequate and healthy eating is crucial, once it will contribute to enhancing TCD4+ lymphocyte levels, improvement of intestinal nutrients absorption, attenuation of health disorders due to a high incidence of gastrointestinal symptoms and even other symptoms [15,28]. Nevertheless, more studies are necessary to evaluate synbiotic use in PLWHA to elucidate questions about dosage, type of strains and their combination, the interaction between nutritional treatment and ART, and viability regarding cost and time of treatment.

5. Conclusions

Diarrhea decreased in both groups, but no statistical difference between treatments was observed. Both treatments, synbiotic supplementation and dietary intervention, reduced gastrointestinal symptoms in PLWHA. The use of synbiotic appeared to reduce a greater number of symptoms although no statistical differences between groups were observed. These findings show the relevance of a nutrition intervention in gastrointestinal symptoms improvement. The positive effects arising from this study from an individualized nutritional treatment proposal reinforces the significance of the nutritionist as a health promoter and as the one responsible for the nutritional treatment of PLWHA.

Table 2
Comparison of incidences of gastrointestinal symptoms in placebo and synbiotic groups at the end of follow-up in HIV-infected patients on ART. Brazil, 2011.

	Placebo n = 25 n (%)	Synbiotic n = 23 n (%)	Percentage difference between groups	p-value[a]
Diarrhea	1 (4.0)	3 (13.6)	9.6	0.24
Nausea and/or vomit	2 (8.0)	2 (8.7)	0.7	0.93
Dyspepsia	4 (16.0)	3 (13.0)	3.0	0.77
Heartburn	4 (16.0)	12 (52.2)	36.2	0.01
Constipation	5 (20.0)	2 (8.7)	11.3	0.27
Flatulence	11 (44.0)	12 (52.2)	8.2	0.57
Three or more gastrointestinal symptoms	3 (12.0)	5 (21.7)	9.7	0.37

[a] Pearson's Chi-Squared test.

Table 3
Incidence of gastrointestinal symptoms in the placebo group at baseline and end of follow-up in HIV-infected patients on ART. Brazil, 2011.

	Baseline n = 32 n (%)	End of follow-up n = 25 n (%)	Percentage difference	p-value[a]
Diarrhea	6 (18.8)	1 (4.0)	−14.8	0.02
Nausea and/or vomit	6 (18.6)	2 (8.0)	−10.6	0.32
Dyspepsia	9 (28.1)	4 (16.0)	−12.1	0.41
Heartburn	22 (68.8)	4 (16.0)	−52.8	<0.01
Constipation	7 (21.9)	5 (20.0)	−1.9	0.70
Flatulence	21 (65.6)	11 (44.0)	−21.6	0.21
Three or more gastrointestinal symptoms	10 (31.2)	3 (12.0)	−19.2	0.10

[a] McNemar's test.

Table 4
Incidence of gastrointestinal symptoms in the synbiotic at baseline and end of follow-up in HIV-infected patients on ART. Brazil, 2011.

	Baseline n = 32 n (%)	End of follow-up n = 23 n (%)	Percentage difference	p-value[a]
Diarrhea	11 (35.5)	3 (13.6)	−21.9	0.01
Nausea and/or vomit	12 (37.5)	2 (8.7)	−28.8	0.01
Dyspepsia	12 (37.5)	3 (13.0)	−24.5	0.10
Heartburn	19 (59.4)	12 (52.2)	−7.2	0.65
Constipation	7 (21.9)	2 (8.7)	−13.2	0.08
Flatulence	13 (40.6)	12 (52.2)	+11.6	0.32
Three or more gastrointestinal symptoms	13 (40.6)	5 (21.7)	−18.9	0.10

[a] McNemar's test.

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Statement of authorship

EAS, MDT, MWN and MOF designed research. ASACS, MOF and MWN conducted research. ASACS and EAS analyzed data and wrote the paper. MWN, MDT and MOF revised the final content of this manuscript. EAS had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that are no conflict of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.06.005.

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