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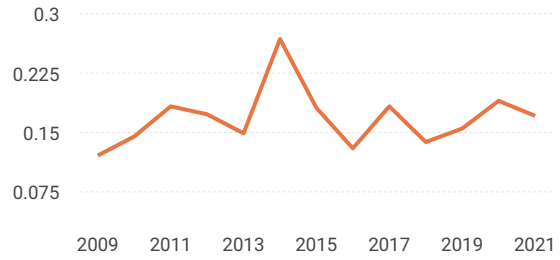

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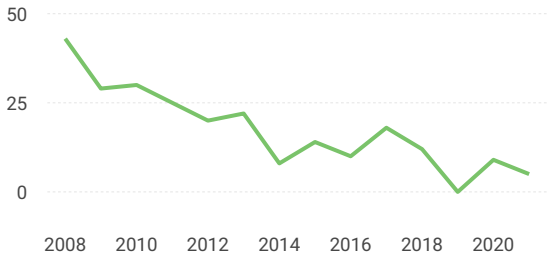

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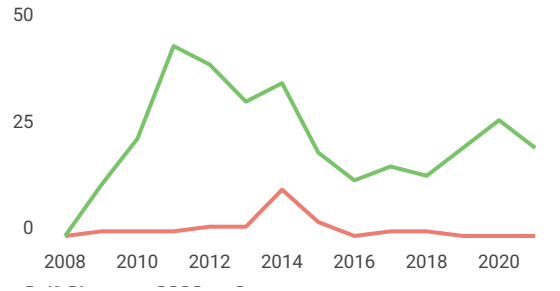

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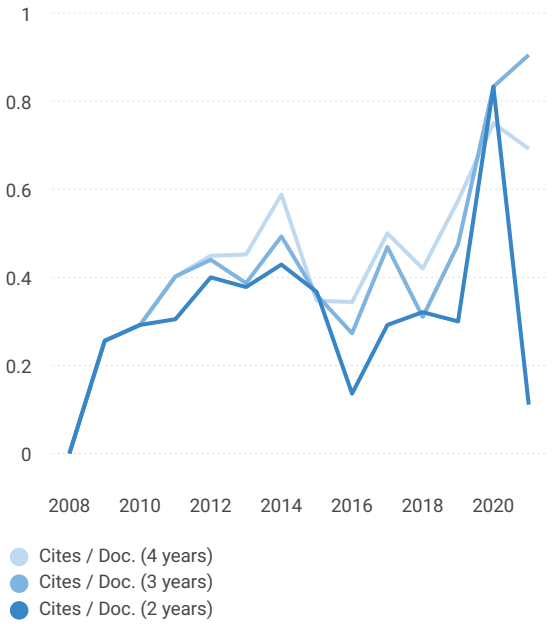

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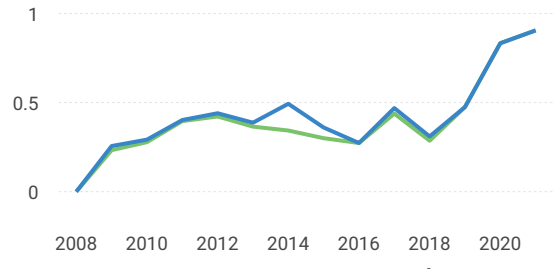

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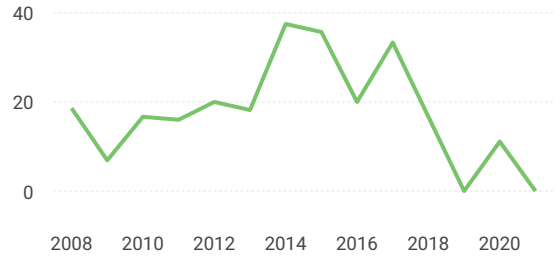

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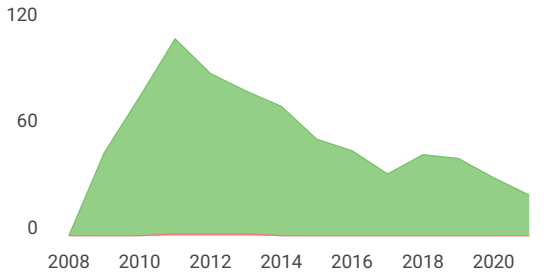

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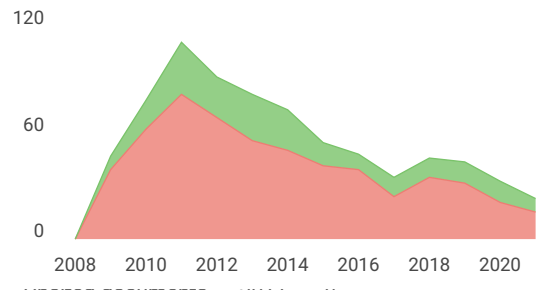

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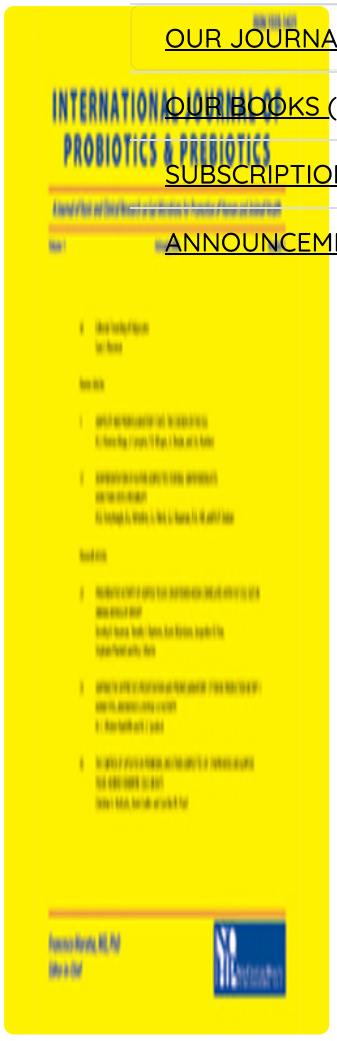

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Clinical Research

Regulation of T Helper and Regulatory T Cells by *Lactobacillus Plantarum* IS-10506 Supplementation to Human Immunodeficiency Virus-Infected Children Under Antiretroviral Therapy

[1,2]Reza Gunadi Ranuh, [1,2]Sitti Radhiah, [1,2]Khadijah Rizky Sumitro, [1,2]Andy Darma, [1,2]Alpha Fardah Athiyyah, [1,2]Dwiyanti Puspitasari, [1,2]Dominicus Husada, [1,2]Anang Endaryanto, [3]Ingrid Surono and [1,2]Subijanto Marto Sudarmo

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Human immunodeficiency virus infection is associated with impairment of T helper 1, T helper 2, regulatory T, and T helper Type 17 homeostasis. While probiotics are widely known to improve these changes, understanding of their role on children's immune system remains limited. In a randomized, double-blind, and placebo-controlled study conducted in Dr. Soetomo General Hospital, Surabaya from December 2012 to March 2013, we have investigated the effect of *Lactobacillus plantarum* IS-10506 on the regulation of T helper and regulatory T cell in children infected with human immunodeficiency virus receiving antiretroviral therapy for at least 6 months. Twenty-one human immunodeficiency virus infected children were divided into placebo and probiotic groups and *L. plantarum* IS-10506 was administered at a dose of 2.86×10^{10} colony forming units/day for 6 weeks. Levels of interferon-γ, interleukin-4, transforming growth factor-β, and interleukin-17 were analyzed before and after treatment as an indicator of T-cell regulation of T helper and regulatory T cells. The results show a significant increase in transforming growth factor-β level ($p = 0.003$) after administration of *L. plantarum* IS-10506 compared to placebo with the first-line antiretroviral therapy group. There was no reported adverse effect in this study. In conclusion, *L. plantarum* IS-10506 increases the regulation of regulatory T cell in human immunodeficiency virus infection in children receiving first-line antiretroviral therapy treatment.

Keywords: ARV, HIV infection, *Lactobacillus plantarum*, Probiotic

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Abbreviations Used: Analysis of variance, ANOVA; Antiretroviral therapy, ARV therapy; Colony forming unit, CFU; Ethylenediaminetetraacetic acid, EDTA; Human immunodeficiency virus, HIV; Interferon-γ, IFN-γ; Immunoglobulin E, IgE; Immunoglobulin G, IgG; Interleukin-17, IL-17; Interleukin-4, IL-4; Transforming growth factor-β, TGF-β; T helper, Th, T; T helper Type 1, Th1; T helper Type 17, Th17; T helper Type 2, Th2; Regulatory T cell, Treg

INTRODUCTION

While the global incidence of pediatric HIV has declined substantially between 2000 and 2018 in children (aged 0–14 years), the number is increasing in many developing countries (Slogrove et al., 2020). However, no more than half of these children receive ARV therapy (Haberer and Mellins, 2009; Imami et al., 2002; WHO, 2010). ARV therapy can maintain viral suppression in HIV-infected patients but does not lead to complete recovery because it still causes chronic immune activation and persistent inflammation associated with impaired homeostasis of Th1, Th2, Treg, and Th17 (Appay and Sauce, 2008; Cassol et al., 2010; Hunt, 2010). Probiotics function as immunomodulators by inducing tolerance immunology (Endaryanto, 2006; Saitoh et al., 2010) that can improve impaired homeostasis of Th1, Th2, Treg, and Th17 (Ancuta et al., 2010; Cross, 2002).

Lactobacillus plantarum strain IS-10506 is one of the local Indonesian probiotic strains isolated from local fermented buffalo milk (Suryanti et al., 2010). This probiotic has been shown to improve impaired homeostasis of Th1, Th2, Th17, and Treg by increasing the number of lymphocytes. Treg directly or indirectly affects the Th1–Th2 balance. Data from Nigeria, Brazil, and Tanzania suggest that probiotics may delay the damage or protect HIV patient's immune function (Anukam et al., 2008; Irvine et al., 2010; Lívia Trois et al., 2008). Probiotics may overcome chronic immune activation in HIV patients by correcting Th1, Th2, Treg, and Th17 homeostasis disorders (d'Ettorre et al., 2015; Bandera et al., 2016). This study was conducted to assess the effect of probiotic *L. plantarum* IS-10506 administration to HIV infected-children receiving ARV therapy on the immune response of Th1, Th2, Treg, and Th17.

MATERIAL AND METHODS

Study Design

This study used a randomized, double-blind placebo-controlled trial (Clinical trial number TCTR20180525003). This study was conducted in intermediate care of Infectious Disease Unit outpatient clinic in Dr. Soetomo General Hospital, Surabaya, Indonesia, from December 2012 to March 2013. Ethical clearance certificate was issued by Dr. Soetomo Hospital Research Ethical Committee (# 217/Panke.KKE/IX/2012 on 18 September 2012). Randomization was conducted independently by simple random number draw by the pharmacist. This method was a part of a previous study (Athiyyah et al., 2019).

Study Subjects

Patients meeting inclusion criteria were recruited from the intermediate care of Infectious Disease Unit outpatient clinic in Dr. Soetomo General Hospital, Surabaya, Indonesia. Inclusion criteria included boys and girls (2–18 years), presence of HIV infection based on the World Health Organization (WHO) criteria with an absolute CD4+ T cells ≥ 350 cells/mm^3 (age ≥ 5 years) or the percentage of CD4+ T cells ≥ 25% (2–4 years), had received antiretroviral therapy at least 6 months before the study. The parents or guardian signed informed consent sheet before following any procedures relating to research. Exclusion criterion was patients who failed ARV and were given supplementation probiotics 2 weeks before this study. Drop out criteria were the subject/parent decided not to continue participating in the study either for medical or nonmedical reasons, did not take probiotics for 2 consecutive weeks, found symptoms of a severe decline in clinical conditions, or severe opportunistic infections.

Treatment Protocol

Subjects were divided into two groups, placebo and probiotic (Fig. 1). We divided the placebo group into placebo with first-line antiretroviral group and placebo with second-line antiretroviral group to compare cytokine levels between these groups. The study used probiotic *L. plantarum* IS-10506 (GenBank accession number DQ860148). The probiotic group was given probiotics prepared aseptically in a powdered form at a dose of 2.86×10^{10} CFU/day. The powder form was packed in an aluminum foil and given orally once daily for 6 weeks. The placebo group received maltodextrin

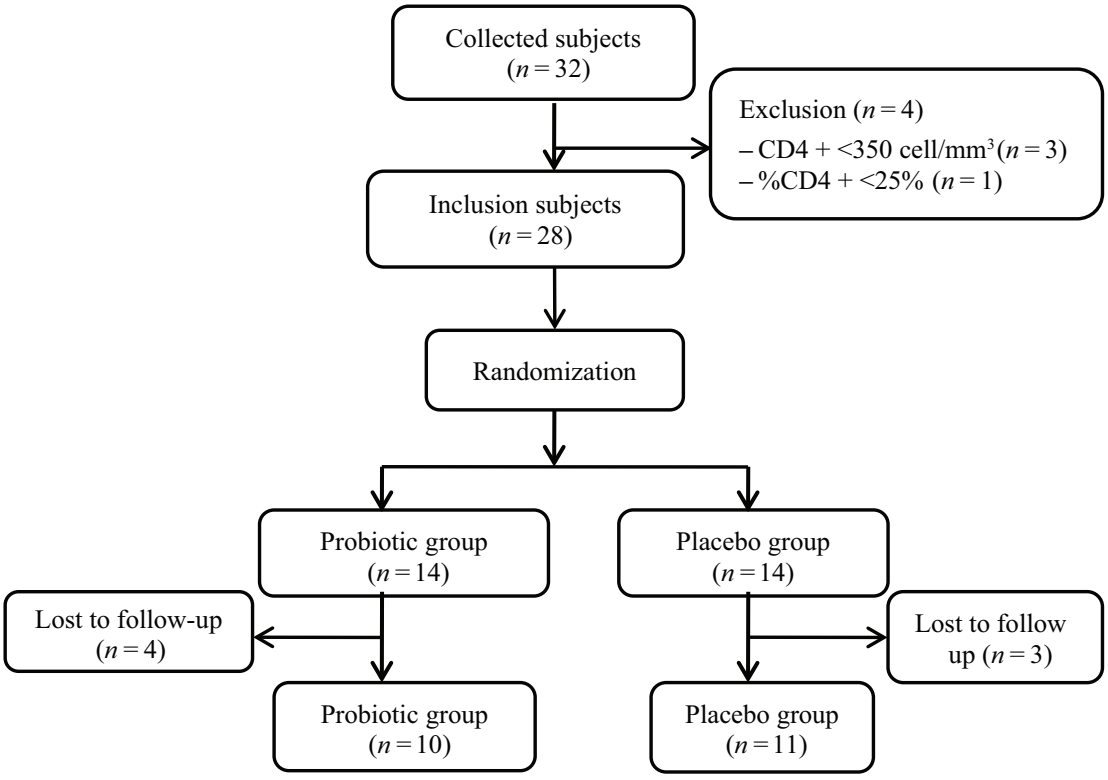

FIGURE 1 | The scheme of subject recruitment.

packaged and flavored exactly like the probiotic, given once a day for 6 weeks. Observation on each subject was conducted over 6 weeks.

Immunological Assays

A 3 mL blood sample was collected in an EDTA tube. The absolute CD4+ T cell count and percentage CD4+ T Cell were analyzed with a flow cytometry (BD FACSCalibur, Canada) using BD reagent (CD4 reagent catalog No. 3480383). Both absolute count and percentage of CD4+ were obtained by calculation. Th1 response immune was determined from IFN-γ level. Th2 response immune was determined from IL-4. Th17 immune response was determined from IL-17 level and Treg was determined from TGF-β. IFN-γ, IL-4, TGF-β, and IL-17 levels were determined using the enzyme-linked immunosorbent assay (ELISA) method (Calbiotech, catalog number SC221A, El Cajon, CA, USA).

Statistical Analyses

We used SPSS 15 for Windows (IBM, New York, USA) for data analyses and described the demographic of subjects according to age, sex, nutritional status, duration, and type of ART. The difference in levels of each cytokine in each group before and after treatment (pre- and post-test) was analyzed using a *t*-test and the changes in cytokine levels in the blood of each group used. One-way ANOVA test was used for statistical analysis. Data were analyzed using a 95% confidence level with $P < 0.05$.

RESULTS

Thirty-two children meeting inclusion criteria participated in this study after signing of the informed consent from their parents/guardians. Four subjects were excluded for a variety of reasons. Twenty-eight remaining children were divided randomly into the treatment and the control groups of 14 per group. (n = 14). No subjects experienced serious symptoms of clinical deterioration or severe opportunistic infections during the study. Seven were lost to follow-up and these subjects were not included in the analysis. The study analysis was performed on 21 subjects, 11 in the control group and 10 in the treatment group, as shown in Fig. 1.

A total of 11 boys and 10 girls participated in this study. The mean ± SD of the children age was 7.2 ± 3.1 years in the placebo group and 7.6 ± 3.1 years in the probiotic group. All children in the placebo group had good nutrition status, whereas 10% of the probiotic group had malnutrition. There was no significant difference in characteristic factors. However, the ARV type showed significant difference. There was hardly any notable difference in initial cytokines level (Table 1).

From the one-way ANOVA test, the increase in TGF-β level was notably different between the placebo and treatment group (Table 2). There was no significant difference in other cytokines. However, the means for IFN-γ, IL-4, TGF-β, and IL-17 in the probiotic groups increased by 20.42 ± 57.19 pg/mL, 4.23 ± 3.14 pg/mL, 93.00 ± 101.02 pg/mL, and 0.89 ± 2.99 pg/mL, respectively. Multiple comparison test (post hoc multiple comparison) exhibited

TABLE 1 | Characteristic of subjects in the control and probiotic groups.

Characteristics	Placebo Groups (n = 11)	Probiotic Groups (n = 10)	p-values
Gender			
Male (%)	7 (63.63)	4 (40)	0.395[b]
Female (%)	4 (36.37)	6 (60)	
Age (year) (mean ± SD)	7.2 ± 3.1	7.6 ± 3.1	0.774[a]
Nutritional status [*n* (%)]			
Good nutrition	11 (100)	9 (90)	0.476[b]
Malnutrition	0 (0)	1 (10)	
ARV type			
First-line	6 (54.54)	10 (100)	0.035[c]
Second-line	5 (45.46)	0 (0)	
Initial cytokine levels (pg/mL)			
IFN-γ pre. mean (SD)	249.80 (57.47)	255.6 (7.46)	0.868
IL-4 pre. mean (SD)	27.34 (6.99)	26.17 (7.46)	0.714
TGF-β pre. mean (SD)	529.31 (210.04)	401.88 (103.59)	0.099
IL-17 pre. mean (SD)	14.13 (2.18)	13.93 (3.45)	0.878

[a] tested using unpaired *t*-test; [b]tested using Chi-square; [c]tested using Fisher's exact

TABLE 2 | Difference of IFN-γ, IL-4, TGF-β, and IL-17 between probiotic and placebo group.

Cytokines (pg/mL)	Placebo + First-Line ARV (n = 6)	Placebo + Second-Line ARV (n = 5)	Probiotic (n = 10)	p-values
IFN-γ (mean ± SD)	4.35 ± 73.34	22.18 ± 12.67	20.42 ± 57.19	0.829
IL-4 (mean ± SD)	–0.70 ± 6.09	0.89 ± 6.30	4.23 ± 3.14	0.155
TGF-β (mean ± SD)	–89.79 ± 134.47	18.00 ± 49.85	93.00 ± 101.02	0.011
IL-17 (mean ± SD)	0.24 ± 3.737	–0.14 ± 2.87	0.89 ± 2.99	0.825

TABLE 3 | Dual comparison test among three groups with the dependent variable changes of TGF-β

Treatment Groups		*p*-values
Probiotic	Placebo + First-line ARV	0.003
	Placebo + Second-line ARV	0.202
Placebo + First-Line ARV	Probiotic	0.003
	Placebo + Second-Line ARV	0.102
Placebo + Second-Line ARV	Probiotic	0.202
	Placebo + First-Line ARV	0.102

a significant difference (P = 0.011) for the cytokine TGF-β (Table 2). Furthermore, the results showed a significant difference (P = 0.003) between the probiotic group and the placebo with the first-line ARV group (Table 3).

DISCUSSION

HIV infection decreases the secretion of Th1 cytokines and Th2 cytokines production. Few of the Th1 cytokines are IL-2 and IFN-γ, while the Th2 cytokines are IL-4, IL-10, and TNF-α (Reuben et al., 2002). ARV decreases IL-4 and IL-10 level after 12 months. On the contrary, TGF-β level is elevated (Osuji, 2018). Th17 cells were increased by the secretion of proinflammatory cytokine IL-17 and depleted in HIV infection (Elhed and Unutmaz, 2010).

In this study, TGF-β increased after probiotic *L. plantarum* IS-10506 administration at a dose of 2.86×10^{10} for 6 weeks in HIV children who were receiving ARV for 6 months. We found significant differences between the probiotics groups and the placebo group combined with first-line ARV. Our data concur with an earlier observation reporting benefits of probiotics in increasing Treg cytokines levels, especially TGF-β that is essential to controlling immune activation (Hummelen et al., 2010). TGF-β can modulate Treg cell responses so the level of Treg also increased (Wan and Flavell, 2007). Probiotics, such as *L. plantarum*, are known to have inducing effect on Treg cell (Smelt et al., 2012). In this study (Smelt et al., 2012), administration of three bacterial strains—two *Lactobacillus* probiotic strains, i.e., *L. plantarum* WCFS1 and *L. salivarius* UCC118, and a nonprobiotic *Lactococcus* strain, i.e., *L. lactis* MG1363—to healthy mice reduced specific splenic T helper cell cytokine responses after ex vivo restimulation. Their data demonstrated that in healthy mice, lactobacilli can balance T cell immunity in favor of a more regulatory status, via both regulatory T cell dependent and independent mechanisms in a strain-dependent manner (Smelt et al., 2012).

Treg cells are essential for the balance between tolerance and immunity (Huang et al., 2020). Treg cells and cytokines resolve T cell immune activation in HIV infection (Freeman et al., 2016). Together they protect mucosal surface against the destruction by inflammatory response through deficiency of TGF-β leading to uncontrolled inflammation at mucosal surfaces (Konkel and Chen, 2011). Decrease in TGF-β level not only disrupts the immune system but also interferes with the development of intestinal microbiota (Bauché et al., 2017). Tregs can also directly reduce the activation of T cells, thus decreasing the number of target cells for HIV replication. Treg can also reduce the capacity of dendritic cells to transmit HIV into CD4 T cells and viral replication by affecting the replication cycle of HIV (Freeman et al., 2016). Therefore, by modulating these pathways Treg may reduce immune activation in ARV-treated patients. However, these processes are not as effective in patients who are not treated with ARV drugs, especially those who have high immune activation. Increasing expression of CD39 on Treg contributes to the occurrence of T cell anergic that worsen the HIV disease (Chevalier and Weiss, 2013).

Our study showed that administration of probiotic *L. plantarum* IS-10506 (2.86×10^{10} CFU/day) did not affect IFN-γ, IL-4, and IL-17 levels in HIV-infected children who received ARV therapy. Our observations are in line with the results of a double-blind, randomized controlled clinical trial conducted on HIV-infected women (n = 65, aged 18–45 years) in which the treatment group was supplemented with probiotic *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (2×10^9 CFU) and the control group was given a placebo. Herein, authors did not find any statistically significant difference in IgE, IgG, IFN-γ, and IL-10 levels before and after treatment between the placebo and probiotic group (Hummelen et al., 2010). The results were also in line with another study using bacteria *Lactobacillus* probiotic. There was no difference in Th1 and Th2 cytokines level after the administration of probiotics. Previous studies have shown increased levels of T cell cytokines in normal subjects but not in immunodeficient patients, such as patients with HIV (González-Hernández et al., 2012). A randomized, double-blind controlled study by González-Hernández was conducted on 20 ARV-naïve participants who were randomly divided to receive a prebiotic, probiotics, a synbiotic, or a placebo for 16 weeks. IL-10 concentrations in plasma were measured by ELISA as anti-inflammatory cytokine, whereas IL-6, TNF-α, and IL-1β as proinflammatory cytokines. There was no difference of IL-1β, IL-10, and TNF-α. However, IL-6 significantly decreased in the synbiotic group (P = 0.016) (González-Hernández et al., 2012).

In this study, subjects did not exhibit adverse reactions, such as fever, nausea, vomiting, abdominal bloating, or diarrhea, and there was no deterioration in clinical signs. However, *Lactobacillus* spp has a low potential to cause infection indicated by a study of bacteremia prevalence caused by *Lactobacillus* spp (Antony, Stratton and Dummer, 1996; Adawi et al., 2002; Klarin et al., 2005; Cunningham-Rundles et al., 2011). Patients with immunocompromised status are generally more susceptible to pathogen infection and higher incidence of opportunistic infections than healthy children. Some research on the safety of probiotics has been conducted and proven probiotics to be safe for use in the immunocompromised group (Wolf et al., 1998; Borriello et al., 2003).

CONFLICT OF INTEREST DECLARATION

The authors state that there are no conflicts of interest to disclose.

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