

# Probiotics in Human Immunodeficiency Virus Infection: A Systematic Review and Evidence Synthesis of Benefits and Risks

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People living with human immunodeficiency virus frequently use dietary supplements, including probiotics, but concern exists about ingesting live organisms. We performed a systematic review of the benefits of probiotics and a meta-analysis of sepsis risk. We undertook a protocol-driven, comprehensive review to identify all relevant studies, assess their quality, and summarize the evidence. Of 2068 references, 27 were analyzed. The data suggest possible benefits for CD4 count, recurrence or management of bacterial vaginosis, and diarrhea management. We examined randomized, controlled studies explicitly assessing sepsis in any patient population, and we found zero cases of supplement-associated bacteremia or fungemia in 39 randomized controlled trials comprising 9402 subjects. The estimated number needed to harm is 7369 in Bayesian approach (95% credible interval: 1689,  $\infty$ ), which should reassure clinicians. No or mild adverse effects were reported. Longer duration studies investigating different individual and mixed strains for plausible indications are needed to establish best practices.

**Keywords.** bacteremia; fungemia; HIV infection; probiotics.

Individuals living with human immunodeficiency virus (HIV) frequently use dietary supplements [1]. The use of probiotics may be inexpensive and potentially clinically important interventions to reduce HIV-related morbidity and mortality [2].

Human immunodeficiency virus infects CD4<sup>+</sup> T lymphocytes and monocyte-derived-macrophages colonizing the gut-associated lymphoid tissue [3]. Significant disruption to gut architecture can occur, with a concomitant release of lipopolysaccharide (LPS) into peripheral blood, correlating with systemic immune activation, a hallmark of HIV disease progression [4]. Probiotics may reduce immune activation and bacterial translocation [5] and possibly reduce acquisition or transmission of infections [6].

This paper expands and updates previous reviews. Level B evidence was found for treating diarrhea; it was not possible to make a recommendation regarding use of probiotics in HIV-infected patients [7]. A meta-analysis in children found evidence for decreased duration of diarrhea and fever but limited data for HIV<sup>+</sup> children [8]. Evidence is fairly robust for the use of

probiotics for primary prevention, with weaker evidence as secondary prophylaxis for *Clostridium difficile* infections [9]. Probiotics may modulate immune function, offset the sequelae of malnutrition, mitigate enteric infections and eventually serve as microbicides or vehicles for mucosal delivery of vaccines [10, 11]. Probiotics may have clinical benefits; however, access remains a limiting factor in some settings [12–14]. Our review adds an HIV-specific focus to a systematic review previously conducted of conditions pathologically similar to HIV [15].

Several case reports document probiotic organisms causing sepsis [16], but no studies provide numerical estimates of risk. Therefore, we assessed data from randomized controlled trials (RCTs) in people with and without HIV where probiotics were administered, and risk of sepsis arising from bacteremia or fungemia was explicitly assessed. We derived a risk estimate and number needed to harm (NNH) using Bayesian analytical methods.

## METHODS

We conducted a systematic review, querying multiple databases, providing a comprehensive overview of the use of probiotics, prebiotics, or synbiotics in HIV disease and a data synthesis of sepsis risk of probiotics. Our protocol was registered with PROSPERO [17].

## SEARCH METHODS

### Eligibility Criteria

We included clinical trials of individuals of any age with documented HIV disease with or without concurrent or active infection, whether or not they were on antiretroviral (ARV) therapy.

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We defined probiotic supplements as commensal bacterial or fungal supplements, in any form, including capsule, tablet, powder, softgel, or fortified food forms. Prebiotics were defined as nondigestible food ingredients that modify intestinal microbiota by enhancing the growth of commensal bacteria [18]. Studies of synbiotics combining prebiotics and probiotics were included.

### Information Sources

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (The Cochrane Library), Cochrane Reviews, Cochrane Trials, AEGIS, AMED, CINAHL, Google Scholar, and the World Health Organization. Searches were conducted from database inception through March 2016.

### Study Selection

Reviewer pairs independently screened citations and abstracts of all publications obtained by the search strategies (Figure 1). Disagreements were resolved by consensus.

### Data Collection Process

For eligible trials, we obtained full articles and assessed their relevance based on the preplanned criteria for inclusion in the systematic review.

### Data Items

We extracted data on study design, intervention, trial design, site, number of participants, inclusion and exclusion criteria,

duration, toxicity/adverse events, primary endpoint, secondary endpoint, findings, baseline differences, conclusions, efficacy, and safety (Table 1).

## QUALITY APPRAISAL

### Risk of Bias of Individual Studies

We evaluated methodological quality with the Cochrane Collaboration's tool for assessing the risk of bias [19], on the basis of sequence generation, allocation concealment, blinding, intention to treat or per protocol analysis, missing data and attrition, and selective reporting. We recorded details of trial design, conflict of interests and sponsor, participant characteristics, interventions and outcome measures (Table 2).

### Risk of Bias Within Studies

Studies were assessed for randomized allocation, allocation concealment and participants, and observer blinding. Two studies were observational [20, 21].

## DATA ABSTRACTION

### Summary Measures

Our primary clinical outcome was the effect on diarrhea. Other outcomes included CD4, microbial translocation, microbicidal effects and bacterial vaginosis (BV). Insufficient data on viral load was available to warrant a separate assessment.

## SYNTHESIS

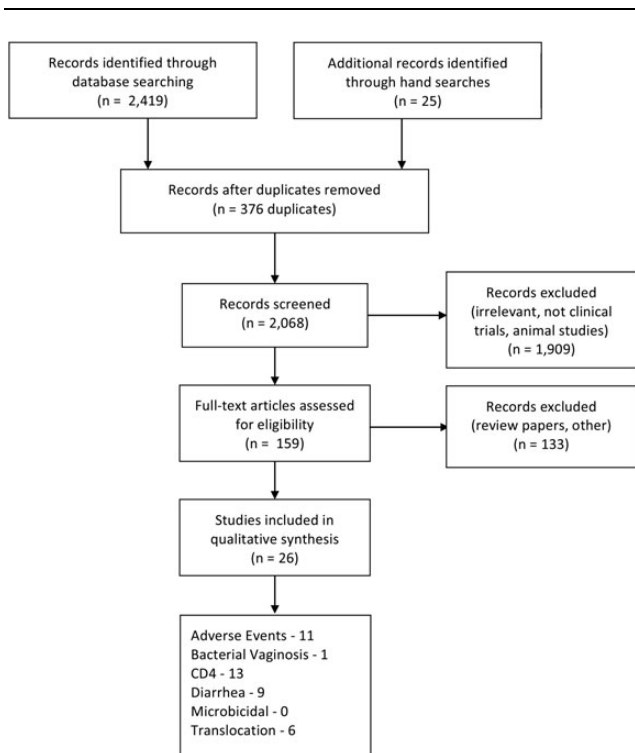
### Sepsis Risk Meta-Analysis

We pooled data from all studies with predefined and explicit reporting on sepsis risk (bacteremia or fungemia) from the use of probiotics, including HIV-negative patients (Supplemental Table). In our Bayesian fixed effects model,  $\pi_i$  denotes the probability of not observing an adverse event in study  $i$  under the placebo condition;  $\rho_i$  denotes the ratio of the probability of non-events in the treatment condition of study  $i$  relative to the probability of nonevent in the placebo condition; therefore, the probability of not observing an adverse event in the treatment condition is  $\rho_i\pi_i$ . The model assumes a priori that the risk of an adverse event is more probable in the treatment condition, so that the probability ratio is contained within the unit interval, ie,  $0 \leq \rho_i \leq 1$ . The model assumes that the probability of an adverse event is constant across studies; hence, it assumes  $\pi_i = \pi$  and  $\rho_i = \rho$  for all studies  $i$ . To reflect lack of knowledge about the parameters, we chose to assume uniform priors on  $\pi$  and  $\rho$ . We approximated the posterior median of the NNH by Markov chain Monte Carlo in OpenBugs. We deemed that a Bayesian random effects analysis would not yield significant differences in our analysis [22].

## RESULTS

### Search Outcome

A total of 2068 titles were identified (see Figure 1). Of these, 27 were pulled for review. The following outcomes were reviewed:



**Figure 1.** Flow chart of selection process of reviewed studies. Studies included add up to more than 26 due to multiple outcomes in some studies.

**Table 1. Probiotics and Prebiotics in HIV: PICOS Study Description**

Reference	Population/ARV	Duration	Intervention/Duration	Comparator	Outcomes (Endpoint) 1°, 2°
Anukam et al [28]	Adult HIV+ women, n = 24 Not on ARV	Over 15 d	Yogurt fermented with specific strains; n = 12	Yogurt with standard strains n = 12	CD4, hematologic parameters, diarrhea duration
Cunningham-Rundles et al [31]	n = 17 Pediatric HIV		<i>Lactobacillus plantarum</i> 299v - 1st child received in a juice; further children received packets	Placebo packet n = unclear	Nutrient status and growth; colonization of gut and immunological effects
Gautam et al [23]	n = 146 HIV+ ≤15 years old Randomized by ARV use	3 mo	<i>Lactobacillus sporogens</i> n = 35 on ARV n = 30 not, MN only n = 25 not, probiotic	Supplement without probiotics n = 31 on ARV; n = 25 not	CD4
Gonzalez-Hernandez et al [3]	RCT; n = 20 5 in each arm, probiotic, prebiotic, symbiotic, placebo ARV naive, HIV+	Over 16 wk	Prebiotic: 10 grams of agavins from <i>Agave tequilana</i> Weber var. <i>azul</i> (FOS with mainly β(2–1) linkages, and some β(2–6) linkages); Probiotic: <i>Lactobacillus rhamnosus</i> HN001, <i>Bifidobacterium lactis</i> Bi-07 at 10 <sup>9</sup> cfu/mL, or Synbiotic combination	Placebo was a product of Biogel without probiotics or prebiotic n = 5	1- Safety, QoL 2- Absolute CD4+ count, cytokine level 3- Viremia, bacterial DNA in plasma and stool, qPCR for bacterial 16S rRNA in plasma and feces, qPCR for <i>Bifidobacterium</i> and <i>Clostridium</i> spp in feces)
Gori et al [18]	n = 57 HIV+ ARV naive Each arm, n = 19	12 wk; follow-up at 16 wk off tx	Prebiotics: 15 (n = 19) or 30 g (n = 19) short-chain galactooligosaccharides, long-chain fructooligosaccharides, pectin hydrolysate-derived acidic oligosaccharides daily	Placebo n = 19	Immune activation (soluble [s]CD14, LPS); impact on commensal and pathogenic bacterial species Flatulence and abdominal distension by week 12 were noted.
Heiser et al [30]	n = 35 HIV+ adults on ARV (nelfinavir-containing regimen) Pilot study	12 wk	Phase 1: Probiotics (1.2 g of acidophilus/bifidus mix) and 12 g/d of soluble fiber first 4 wk; Phase 2 added in 10/g day titrated up to 30 g/day within 1 wk of L-glutamine ("S" group) n = 28 in S (active)	Standard of care ("C") n = 7	Diarrhea-primary CD4, HIV VL-secondary
Hemsworth et al [41]	n = 25 Adult HIV+ pilot study On ARV	30 d each tx; 14 d washout	MN and probiotic (A), MN alone (B) and probiotic alone (C). ABC, BCA, or CBA A: MN plus <i>Lactobacillus rhamnosus</i> CAN-1 (minutes 10 <sup>9</sup> cfu/mL); B: MN alone; and C: <i>L. rhamnosus</i> CAN-1 (minutes 10 <sup>9</sup> cfu/mL).	3-arm crossover design	No single primary outcome stated; effects on immune status, bowel health, and QoL
Hummelen et al [29]	n = 65 (see also next entry)	25 wk (6 mo)	<i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 n = 32	Placebo n = 33	To prevent or cure bacterial vaginosis
Hummelen et al [46]	n = 65, women HIV+ ARV naive	25 wk	Oral capsules <i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 n = 32 probiotics	Placebo n = 33	CD4, immune markers, diarrhea; effect on bacterial vaginosis
Hummelen et al [36]	N = 112 Adult (>18) HIV+ ARV naive	4 wk	MN fortified yogurt with <i>L. rhamnosus</i> GR-1 n = 55	a MN fortified yogurt without additional probiotic <i>L. rhamnosus</i> GR-1 (n = 57) for 4 wk	CD4 Secondary outcomes: hematology indicators (creatinine, albumin, ALT, and full blood count), incidence of diarrheal episodes, symptoms, physical energy and their ability to perform activities of daily living.
Irvine et al [38]	n = 150 HIV+ Mixed ARV use.	3 y	Probiotic yogurt consumption. n = 68 on probiotics	Not consuming the yogurt. n = 82	CD4 count; prophylactic effect on diarrhea
Irvine et al [21]	n = 171 Adult HIV+ approximately 60% on ARV	3 y (see above)	Plain yogurt supplemented with the probiotic strain <i>L. rhamnosus</i> GR-1 (Fiti) as an adjunct to the diet; patients on ARV n = 85	Not consuming probiotic yogurt rather maize flour, beans n = 86	GI health, QoL, and immune function.

Table 1 continued.

Reference	Population/ARV	Duration	Intervention/Duration	Comparator	Outcomes (Endpoint) 1°, 2°
Kerac et al [24]	795 children with severe acute malnutrition (age range, 5–168 mo) HIV <sup>+</sup> : 170/399 (42.6%) Few on ARV	Median 33 d	Synbiotic2000 Forte (Medipharm AB, Kagerod, Sweden): 10 <sup>11</sup> cfu total of mix of <i>Pediococcus pentosaceus</i> 16:1 LMG P-20608, <i>Leuconostoc mesenteroides</i> 23–77:1 LMG P-20607, <i>Lactobacillus paracasei</i> subsp <i>paracasei</i> F-19 LMG P-17806, and <i>L plantarum</i> 2362 LMG P-20606 plus prebiotic fibres (2.5 grams of each per 10 <sup>11</sup> bacteria) (oat bran [rich in β-glucans], inulin, pectin, and resistant starch).	Standard RUTF HIV <sup>+</sup> 192/396 (48.5%)	Nutritional cure (weight-for-height >80% of National Center for Health Statistics median on 2 consecutive outpatient visits). Secondary outcomes included death, weight gain, time to cure, and prevalence of clinical symptoms (diarrhea, fever, and respiratory problems).
Saint-Marc et al [20]	n = 17 with various serious OIs, stage IV disease	15 d	<i>Saccharomyces boulardii</i> n = 17	None	Impact on diarrhea; weight
Saint-Marc et al [33]	n = 35 HIV <sup>+</sup> All pts on AZT, stage IV disease	7 d	<i>S boulardii</i> ; 2 500-mg sachets n = 18	Placebo n = 17	Impact on diarrhea
Salminen et al [35]	n = 17 HIV <sup>+</sup> On ARV (20 enrolled; 1 lost to f/u after first period; 2 before randomization)	2 wk	<i>L rhamnosus</i> GG caps, 1–5 × 10 <sup>10</sup> cfu n = 17	Placebo n = 17 (crossover)	Primary GI symptoms/diarrhea; VAS 0–100 mm CD4, HIV load monitored
Schunter et al [42]	N = 33 HIV <sup>+</sup> women on ARV	4 wk	Synbiotic 2000 (see Kerac et al [24] entry) n = 14	Fiber-only placebo n = 13 (PP)	Microbial translocation; cellular activation; plasma and fecal bacterial levels
Trois et al [34]	N = 77 RCT, HIV <sup>+</sup> children; 48.6% (probiotics) and 61.5% (placebo) on ARV; 62.2% and 48.7% in probiotics and placebo arms, respectively, were using didanosine	2 mo	Standard formula containing <i>Bifidobacterium bifidum</i> with <i>Streptococcus thermophilus</i> —2.5 × 10 <sup>10</sup> cfu in 100 mL milk. n = 38	Placebo (14 g formula diluted in 100 mL of milk) daily throughout a 2-month period. n = 39	1- CD4 2- The quality and number of stools assessed by questionnaire (watery to normal stool consistency, number of stools passed during a 24-h period).
Villar-García et al [26]	n = 44 HIV <sup>+</sup> Stable ARV, VL < 20 for at least 2 y	12 wk w/12 wk follow-up	<i>S boulardii</i> , 6 × 10 <sup>7</sup> living “bacteria” n = 22	Placebo n = 22	Translocation: change of LBP Other markers of translocation, CD4
Wolf et al [37]	n = 39 HIV <sup>+</sup> Most not on ARV.	21 and 35 d study	<i>L reuteri</i> n = 21	Placebo n = 18	Safety, tolerability. Secondary: serum chemistry, hematology, immune profile, urinalysis, physical examination, GI tolerance and fecal microbiota data.
Yang et al [39]	N = 17 HIV <sup>+</sup> CD4 ≥ 250 Population is Adults; all on ARV	3 mo	2 billion <i>Bacillus coagulans</i> GBI-30, 6086 n = 10	No subsps n = 7	Residual gut inflammation. Gastrointestinal Symptom Rating Scale administered monthly. Viremia, CD4 <sup>+</sup> T-cell percentage/concentration, sCD14, soluble intestinal fatty acid binding protein, sCD163, D-dimer, CRP, IL-8, and tumor necrosis factor-α.

Abbreviations: ALT, alanine transaminase; ARV, antiretroviral; AZT, azidothymidine; β<sub>2</sub>M, beta-2-microglobulin; cfu, colony-forming unit; CRP, C-reactive protein; DNA, deoxyribonucleic acid; FOS, fructooligosaccharide; f/u, follow up; GI, gastrointestinal; HIV, human immunodeficiency virus; IL, interleukin 6; ITT, intent to treat; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; MN, micronutrient; OI, opportunistic infection; PICOS, patient/problem intervention comparison outcome setting; PP, per protocol; pts, patients; QoL, quality of life; qPCR, quantitative polymerase chain reaction; RCT, randomized controlled trial; rRNA, ribosomal ribonucleic acid; RUTF, ready-to-use therapeutic food; tx, treatment; VAS, Visual Analogue Scale; VL, viral load.

**Table 2. Probiotics and Prebiotics in HIV: Methodological Quality of Studies<sup>a</sup>**

Reference	Primary Endpoint	Study Design	Selection Bias	Performance Bias	Detection Bias	ITT/PP	Comments
Anukam et al [28]	Moderate diarrhea	DB CT	I	I	Unclear	PP	No randomization or allocation described. Research funded in part by Urex Biotech Inc. and Natural Sciences and Engineering Research Council of Canada.
Cunningham-Rundles et al [31]	Nutrient status and growth; colonization; immune effects	Observational case study; DB RCT	I	I	I	PP	Although 17 participants initially enrolled, only in a later description was it stated parents or children chose between identical packets (Cunningham-Rundles et al [31]). Of these, 14 were evaluable and 5 received placebo packets.
d'Ettorre, et al [43]	Inflammation and translocation	Observational	N/A	N/A	N/A	N/A	Comparator arm was 11 HIV-negative individuals given the 1 g probiotics bid. Bloodwork was done in each group (but not CD4 counts in the HIV- group).
Falasca, et al [40]	Inflammation and translocation	Observational	N/A	N/A	N/A	N/A	No comparator arm. 30 HIV+ men on ARV.
Gautam et al [23]	CD4, pediatric	RCT	A	I	I	PP	Randomization by using colored cards in white envelopes. Not blinded; participants received probiotic, MN syrup or sachets.
Gonzalez-Hernandez et al [3]	Safety, CD4, translocation	DB RCT	U	U	A	ITT	Explicit commentary on randomization and blinding methods lacking; analysis appeared to be ITT but not explicitly stated. The placebo was a product of Biogel without probiotics or prebiotic, but with the same flavor and characteristics.
Gori et al [18]	Soluble (s)CD14, LPS; effect on bacterial load in feces	DB RCT	U	A	A	ITT, PP	"Subjects were randomized in three groups . . ." but no further description. There may be conflicts of interest. Safety monitoring is not described.
Heiser et al [30]	Diarrhea from protease inhibitors	Randomized, not blinded	U	I	I	PP	Randomization not described; unblinded study (observational/pilot study). Glutamine added at week 4 only for treated group.
Hemsworth et al [41]	Immune status, bowel health, QoL	DB RCT, crossover	A	A	A	ITT, model	One dropped out within the first month.
Hummelen et al [46]	Bacterial vaginosis	DB RCT	A	A	A	ITT	Possible conflict of interest.
Hummelen et al [29]	CD4	DB RCT	A	A	A	PP	Dr. Reid no longer holds patents for the use of <i>Lactobacillus</i> GR-1 and RC-14. Chr Hansen provided capsules; financial support from Danone Institute Canada, AFMnet.
Hummelen et al [36]	CD4	DB RCT	A	A	A	ITT	It appears 3 early withdrawals were treated as data carried forward.
Irvine et al [21]	GI health, QoL, immune function.	Observational, retrospective	N/A	N/A	N/A	N/A	Observational.
Kerac et al [24]	Primary outcome was nutritional cure	DB RCT	A	A	A	ITT	33-day study. No sepsis seen but investigated. Cure as weight-for-height >80% of National Center for Health Statistics median on 2 consecutive outpatient visits.
Saint-Marc et al [20]	Diarrhea; weight	Observational	N/A	N/A	N/A	N/A	Preliminary observational study.
Saint-Marc et al [33]	Diarrhea	DB RCT	A	A	A	ITT	One patient was precluded from taking doses due to a cerebral toxo-induced coma.
Salminen et al [35]	Primary GI symptoms, diarrhea.	DB RCT crossover	A	I	U	PP	This study was financially supported by Valio Ltd., Helsinki, Finland. 14-day washout period between treatment periods.
Schunter et al [42]	Translocation; cellular activation	DB RCT	A	A	A	PP	No adverse events or side effects reported or mentioned.
Trois et al [34]	Diarrhea; CD4	DB RCT	U	A	U	ITT	Randomization by "cast lots" and products "blinded by a person" not involved in the study.

Table 2 continued.

Reference	Primary Endpoint	Study Design	Selection Bias	Performance Bias	Detection Bias	ITT/PP	Comments
Villar-García et al [26]	Translocation	DB RCT	A	A	A	ITT, PP	12 wk of trial with a subsequent 12-week follow-up. Computer-generated list; all blinded. IL-6 unaffected in ITT analysis but reduced in per protocol analysis.
Wolf et al [37]	Safety and tolerability	DB RCT	A	A	A	PP	Baseline information incomplete. Investigator could determine who received probiotics: less fecal odor, better consistency was observed. Packets were processed and coded (to maintain a double mask) by Anderson Packaging (Rockford, IL)
Yang et al [39]	Residual gut inflammation	DB RCT	I	I	A	PP	Randomization not described. Allocation not described nor was the placebo described. There may be conflicts of interest.

Abbreviations: A, adequate; DB CT, double-blind controlled trial; DB RCT, DB randomized CT; GI, gastrointestinal; HIV, human immunodeficiency virus; I, inadequate; IL, interleukin; ITT, intent to treat; LPS, lipopolysaccharide; MN, micronutrient; N/A, not applicable; PP, per protocol; QoL, quality of life; U, unclear.

<sup>a</sup> Selection bias indicates how interventions were allocated and the randomization process used; performance bias describes the method used to conceal interventions/placebos; and detection bias assesses whether the provider, participant, or outcome assessor could distinguish intervention from comparator.

diarrhea (9); adverse events (11); BV (1); CD4 count (14); and translocation (6) (Figure 1 and Table 3).

Studies included patients on ARVs, patients not on ARVs, and a few patients had mixed use of ARV therapy. In general, descriptions of which ARVs were used were not available (eg, [21, 23–26]). Populations included adult and pediatric studies.

#### Risk of Bias

Publication bias analysis was precluded by the small numbers of studies [27]. We found no evidence of selective reporting or conflicts of interest; however, some studies were funded by nutritional supplement or yogurt companies (Table 2).

#### Impact on Human Immunodeficiency Virus- or Antiretroviral-Associated Diarrhea

Nine studies evaluated various probiotic formulas for diarrhea. Of these, 1 showed mixed benefit, 3 reported benefit, 2 reported no benefit, 1 reported prophylactic benefit, and 2 no reported prophylactic effect. Outcomes varied in terms of frequency of stools, consistency, duration, hospital stay, and use of concomitant antimicrobials and other medications to control diarrhea. Populations varied in age (pediatric/adult) as well as ARV use. Trial duration varied from as little as 2 weeks to 3 years, with the majority of studies lasting 2–25 weeks. On those not yet on ARV, one 2-week study showed benefit [28], whereas a 25-week [29] and 33-day pediatric study showed no benefit [24].

Among those using ARV therapy, a 3-year study assessing probiotic-fortified yogurt saw symptom alleviation and improved work productivity [21]. A 12-week study that included fiber and glutamine found benefit in terms of resolution or reduction in number of stools with decreased loperamide use [30]. Although seeing resolution of diarrhea in an initial case, a further study to assess safety in pediatric populations was undertaken. This study among congenitally infected children

showed that *Lactobacillus plantarum* 299v colonized the gut during use, and for younger children there was some improvement in offsetting energy while potentially offsetting failure to thrive as assessed by growth rates [31, 32]. Two studies investigating *Saccharomyces boulardii* among very ill patients with acquired immune deficiency syndrome observed significant benefit [20, 33].

A pediatric study, where half were on stable ARV at baseline, saw no differences between arms using formula [34]. A 2-week study showed no benefit with more fecal incontinence experienced by the treated group ( $P = .5$ ) [35].

In summary, overall data are inconclusive for a role of bacterially based probiotics for managing HIV-associated diarrhea; however, more studies are needed to determine whether higher doses or combinations of bacterial species may have benefit. The use of the fungal *S. boulardii* may have some benefit.

#### Impact on CD4 Count/Immunological Impact

Fifteen studies reported CD4 counts at baseline and end of study. In 4 studies among ARV-naive patients, 2 found benefit, 1 found no benefit, and 1 reported increases in CD4 in treatment group and declines among placebo recipients that were not statistically significant. Among 7 studies on HIV<sup>+</sup> patients on ARV, 4 reported benefit and 3 did not. Two studies with mixed populations on or not on ARV showed a modest increase in CD4 count. Two pediatric studies showed positive effect [8, 19].

Four studies evaluated patients not on ARV, with moderate changes over relatively short periods. The largest effect was an increase of 102 CD4 cells over 16 weeks in a synbiotic arm compared with control in a small study investigating the impact of such interventions on markers of microbial translocation and inflammation [3]. A 30-day study observed, on average, a 3- to 4-fold improvement compared with controls ( $P < .02$ ) [28].

**Table 3. Probiotics and Prebiotics in HIV: Summaries by Outcome**

Reference	Population	Duration	ARV	Effect	Results
<b>Diarrhea</b>					
Anukam et al [28]	Adult HIV <sup>+</sup> women, n = 24	15 d	–	+	Diarrhea with flatulence and nausea: At 30 d, probiotic group only 4 of 12 had moderate diarrhea, whereas 8 of 11 (73%) did in the probiotic group (no <i>P</i> value). Resolution of other GI symptoms reported in the probiotic group but not the control. The effect disappeared at the 3-month follow-up without treatment.
Cunningham-Rundles et al [31]	n = 17; Pediatric HIV	1 month/2 wk	+	+	Case report: One 11-year-old child with failure-to-thrive on AZT saw after 1-month use resolution of mouth ulcers, candidiasis, and diarrhea; improved appetite; weight gain continued 142 d posttreatment. RCT: Colonization observed by 2 wk of use; subsequent decline approximately 1 mo after stopping. Most children were anergic at BL; supplementation resulted in a positive immunological effect, generally within 1 month. No flatulence or other side effects/AE were observed.
Gonzalez-Hernandez et al [3]	RCT; n = 20; 4 arms; HIV <sup>+</sup> adults	16 wk	–	–	5 patients in each arm, probiotic, prebiotic, synbiotic, placebo. Two patients experienced diarrhea in the placebo and diarrhea arms; 1 in the synbiotic arm; none in the prebiotic arm.
Heiser et al [30]	n = 35; Pilot study; HIV <sup>+</sup> adults with diarrhea	12 wk	+	+	Diarrhea completely resolved in 10 of 28 (36%) subjects (S). Mean ( $\pm$ SD) number of stools/day declined ( $3.40 \pm 1.25$ – $2.54 \pm 1.34$ ; <i>P</i> < .01). Loose, watery stools/day declined in S from $2.84 \pm 1.42$ to $0.74 \pm 1.03$ ( <i>P</i> < .0001). For 15, stools/day decreased from $4.08 \pm 1.35$ to $3.06 \pm 1.68$ ( <i>P</i> < .05) after starting glutamine. In C, stools/day, $4.14 \pm 4.86$ – $3.44 \pm 1.68$ ( <i>P</i> = .678) and incidence of diarrhea was unchanged. In S, loperamide use decreased from $1.69 \pm 2.34$ to $0.31 \pm 0.69$ mg/day ( <i>P</i> < .01); 18 vs 8 subjects used loperamide at 0 and 12 diarrhea/day, $3.00 \pm 4.82$ – $1.36 \pm 1.29$ ( <i>P</i> = .361). Regimen with nelfinavir or lopinavir/ritonavir.
Hummelen et al [46]	n = 65, women	25 wk	–	+	13 of 51 (26%) participants experienced diarrhea for at least 1 day during the intervention. Median number of days similar in both groups and low in both groups (2 days in the placebo group/median 151 days recorded vs 5 days in the probiotic group/148 day recorded) ( <i>P</i> = .4). Adverse event: Control: 2 diarrhea, 1 constipation, 3 nausea, 2 itching or peeling skin, 1 dizziness, and 1 vaginal odor. Probiotics: none reported having diarrhea; 1 abdominal discomfort; 3 nausea; 1 vomiting.
Hummelen et al [36]	N = 112; Adult (>18) HIV <sup>+</sup>	4 wk	–	(+)	Adverse event: Control: 3 reported having diarrhea. Probiotics: 1 reported having diarrhea. No difference between groups was detected in incidence or duration of diarrhea or clinical symptoms. An improvement of hemoglobin levels was observed for all subjects, based upon a mean difference from baseline of 1.4 g/L (SD = 6) ( <i>P</i> = .02).
Irvine et al [38]	n = 150 HIV <sup>+</sup> adults	3 y	±	+	Among those consuming yogurt, 56 of 67 (84%) participants did not report any diarrheal symptoms vs 57 of 82 (69%) participants among the nonconsuming group ( <i>P</i> = .05). Alleviated GI symptoms, improved work productivity, nutritional intake, and tolerance to ARV. See next entry.
Irvine et al [21]	n = 171; adult HIV <sup>+</sup>	3 y (see above)	± approximately 60% on ARV	–	No effect on incidence of diarrhea ( <i>P</i> = .1). Clinical: Median 2 h more work daily ( <i>P</i> = .01), experienced a lower fever incidence ( <i>P</i> = .01), and were more likely to achieve daily nutrient requirements for vitamin A, several B complex vitamins, and calcium ( <i>P</i> = .002); less ARV-related stomach pain ( <i>P</i> = .02) and less GI symptoms that affect daily life ( <i>P</i> = .03).
Kerac et al [24]	795 severely malnourished children	Median 33 d	– (+); Few on ARV.	–	Primary outcome: No effect on prespecified nutritional or clinical outcomes from severe acute malnutrition. Children with severe acute malnutrition (age range, 5–168 mo); HIV <sup>+</sup> : 170 of 399 (42.6%). Inpatient synbiotic users had longer duration of severe diarrhea. Outpatients had less severe diarrhea, but this was not statistically significant ( <i>P</i> = .07).
Saint-Marc et al [20]	n = 17 HIV <sup>+</sup> adults	15 d	?	+	Weight gain of approximately 8 kg observed; resolution of liquid diarrhea in the majority (16 of 17) and normalization of bowel in 4. CD4 count mentioned but outcomes not noted. Patients diagnosed with various serious OIs, stage IV disease.
Saint-Marc et al [33]	n = 35 HIV <sup>+</sup> adults	7 d	+	+	Resolution of diarrhea in 61% of S.b. recipients vs 12% placebo ( <i>P</i> < .002); stool number, weight and volume also improved in S.b. group. CD4 not evaluated. All patients on AZT, stage IV disease.
Salminen et al [35]	n = 17 HIV <sup>+</sup> adults	2 wk	+	–	Diarrhea: no effect on stool frequency or stool consistency. 41% on treatment vs 29% on placebo reported fecal incontinence ( <i>P</i> = .5). No AE or side effect-related withdrawals; no bacteremia reported. (20 enrolled; 1 lost to f/u after first period; 2 before randomization.)

Table 3 continued.

Reference	Population	Duration	ARV	Effect	Results
Trois et al [34]	N = 77 HIV <sup>+</sup> children	2 mo	±	(+)	Formula feeding seemed to improve bowel function; added probiotics slightly improved reduction in liquid stools but not statistically significant. Didanosine may have blunted response. 48.6% (probiotics) and 61.5% (placebo) on ARV; 62.2% and 48.7% in probiotics and placebo arms, respectively, were using ddl
Wolf et al [37]	n = 39 HIV <sup>+</sup> adults	21 and 35 d study	–/some +	–	Bowel function or symptoms: no effect; <i>L. reuteri</i> may be fed to HIV-positive individuals at $1 \times 10^{10}$ cfu/day “without any clinically significant safety or tolerance problems.”
<b>CD4</b>					
Anukam et al [28]	Adult HIV <sup>+</sup> women, n = 24	15 d	–	+	8 of 12 subjects at day 15 and 10 of 11 at day 30, who consumed the probiotic yogurt, had an increase in CD4; placebo $347.25 \pm 76.81$ –30 d change $-2.2$ ; Tx $359.9 \pm 70.1$ –30 d change $+6.7$ (mean values)
d’Ettorre et al [43]	Adult HIV <sup>+</sup> ; n = 11	48 wk	+	+	A weak increase in CD4 percentages and absolute numbers among HIV-1-infected patients between T0 and T1 was observed (respectively $26.45 \pm 10.46$ and $28.1 \pm 8.62$ , $P = .065$ ) with median recovery of 65 cell/ $\mu$ L.
Falasca et al [40]	Adult HIV <sup>+</sup> ; n = 30	4 wk	+	(+)	Average increase $45.9 \pm 35.2$ cells/ $\mu$ L ( $732.2 \pm 208.1$ vs $778.1 \pm 286.8$ cell/ $\mu$ L, $P = .154$ ). No control arm. Effect was not statistically significant.
Gautam et al [23]	n = 146 HIV <sup>+</sup> $\leq 15$ years old	3 mo	±	+	BL CD4 was over 600. Not on ARV, children 5–15 saw a +65 increase in probiotic arm (n = 20) vs –88 decline in control (n = 25; $P = .0022$ ). WHO stage improved in probiotics arm ( $P = .02$ ). On ARV, there was no effect on WHO stage of disease or BMI. Similar decreases in CD4 were seen in both groups on ARV. Patients randomized by ARV use
Gonzalez-Hernandez et al [3]	RCT; n = 20	16 wk	–	+	5 patients in each of 4 arms. The synbiotic group had greatest CD4 increase ( $+102$ ; $P = .05$ ); IL-6 decreased significantly ( $P = .016$ ).
Gori et al [18]	n = 57 HIV <sup>+</sup> Each arm, n = 19	12 wk; f/u 16 wk	–	–	No effect on CD4 changes in any arm (prebiotics only).
Heiser et al [30]	n = 35; pilot study	12 wk	+	+	Placebo BL $-320 \pm 237$ –wk12 $441 \pm 171$ NS; Tx BL $-468 \pm 306$ –wk12 $590 \pm 292$ ( $P < .01$ ); (regimen with nelfinavir or lopinavir/ritonavir)
Hemsworth et al [41]	n = 25; Adult HIV <sup>+</sup> pilot study	30 d each tx; 14 d washout	+	(+)	n = 21 for data: Mean CD4; a mean change of +19 cells/ $\mu$ L (SD = 142); B mean change +41 cells/ $\mu$ L (SD = 221). C a mean change of –7 cells/ $\mu$ L (SD = 154); ( $P$ all $> .05$ ); Overall: There was an overall increase in CD4 by +9 cells/ $\mu$ L, and the frequency of participants with a CD4 count below 200 dropped from 5 to 3. Subjects reported improved energy
Hummelen et al [46]	n = 65, women	25 wk	–	+	BL→10 wk. Average –3 CD4 cells/ $\mu$ L (95% CI, –97 to 91) with placebo vs +50 (95% CI, –61 to 162) probiotics ( $P = .5$ ). BL→25 wk. CD4 +19 cells/ $\mu$ L (95% CI, –90 to 129) placebo vs probiotics +46 cells/ $\mu$ L (95% CI, –100 to 192; $P = .8$ ). Stratified: CD4 = 200–350 placebo mean increase of 34 cells (95% CI, –37 to 105) vs probiotics +158 cells/ $\mu$ L (95% CI, 35–281) at 10 weeks ( $P = .1$ ). CD4 < 200: 4 on probiotics mean increase of 93 cells/ $\mu$ L (95% CI, 26–159) vs mean decrease of 69 cells/ $\mu$ L (95% CI, –95 to –42) ( $P = .04$ ) of 2 on placebo.
Hummelen et al [36]	N = 112; Adult (>18) HIV <sup>+</sup>	4 wk	–	–	MN + probiotic: BL→4 wk: average decline in CD4 count of –70 cells/ $\mu$ L (95% CI, –154 to –15); MN alone: –63 cells/ $\mu$ L (95% CI, –157 to –30; $P = .9$ ).
Irvine et al [21]	n = 171; Adult HIV <sup>+</sup>	3 y	± approximately 60% on ARV	+	Average increase in CD4 of 0.13 cells/mL per day (95% CI, .07–.20; $P \leq .001$ ). Yogurt consumers experienced an additional increase of 0.28 cells/mL per day (95% CI, .10–.46; $P = .003$ ). Adjusting for length of time on ARV: +0.17 cells/mL per day (95% CI, .01–.34; $P = .04$ ).
Kerac et al [24]	795 children HIV <sup>+</sup> : 170/399 (42.6%)	Median 33 d	– (+); few on ARV	–	CD4 taken at first outpatient visit, 2 wk after discharge from ward, seropositive children with severe acute malnutrition (age range 5–168 mo); CD4 < 20% (of seropositive children in whom CD4 taken); Synbiotic 61 of 92 (66.3%); Control 67 of 103 (65.0%); Synbiotic CD4% (mean) $18.3 \pm 9.6$ (n = 92); Control $17.8 \pm 10.1$ (n = 103)
Salminen et al [35]	n = 17 HIV <sup>+</sup> On ARV	2 wk	+	0	$362 \pm 249$ and $362 \pm 239$ at end of study. Crossover design may blunt effect if initial treatment with GG persists longer than 2 wk. 20 enrolled; 1 lost to f/u after first period; 2 before randomization.
Schunter et al [42]	N = 33 HIV <sup>+</sup> women on ARV	4 wk	+	–	CD4: Placebo - BL 627 (SD = 293); Day 28–619 (337); Probiotic–683 (259); Day 28–697 (296) ( $P = .862$ )



Table 3 continued.

Reference	Population	Duration	ARV	Effect	Results
Trois et al [34]	N = 77 HIV <sup>+</sup> children	2 mo	±	+	Mean CD4: count increased in the probiotics group and a small decrease in the control group ( $P = .049$ ). Probiotics—BL 673 (528, 962); end of study: 791 (509, 951); Placebo—BL 580 (337, 821); end of study: 538 (332, 789); $P = .35$ ; $\Delta \log_{10}$ CD4 Probiotics 0.04 ( $\pm 0.19$ ); placebo $-0.26$ ( $\pm 0.16$ ); $P < .048$
Villar-García et al [26]	n = 44 HIV <sup>+</sup>	12 wk	+	–	No effect on CD4 count (12 wk on treatment and at 12 wk follow-up). Patients received stable ARV, VL < 20 for at least 2 yr
Wolf et al [37]	n = 39 HIV <sup>+</sup>	21 and 35 d study	–/some +	–	CD4 Placebo —Day 0—441 $\pm$ 31; Day 21—467 $\pm$ 34—intervention ended; Day 35—484 $\pm$ 34; <i>L. reuteri</i> —Day 0—498 $\pm$ 39; Day 21—461 $\pm$ 46—intervention ended; Day 35—433 $\pm$ 33 ( $P = .05$ at d35 between arms)
Yang et al [39]	N = 17 HIV <sup>+</sup> CD4 $\geq$ 250	3 mo	+	+	CD4: $-81$ to $+315$ (median + 31) cells/mm <sup>3</sup> for placebo; $-109$ – $+232$ (median + 25) cells/mm <sup>3</sup> for the probiotic; CD4% median increased; $-1.8\%$ (range $-7.5\%$ to $+3.7\%$ ) placebo vs $+2.8\%$ (range $-1.5$ to $+4.7\%$ ) probiotic ( $P = .018$ ). CD4 <sup>+</sup> T-cell slopes over prior year were similar, but the percentages increased more in the probiotic group compared with the placebo group. No other biomarker changes except a $P = .05$ observed drop in sCD163. No adverse events: “safe and well tolerated.”
<b>Bacterial Vaginosis</b>					
Hummelen et al [46]	n = 65	25 wk (6 mo)	–	(+)	Cure of BV unaffected but may act as a prophylaxis against recurrence.
Hummelen et al [29]	n = 65, women	25 wk	–	(+)	Supplementation did not enhance the cure of BV among women living with HIV, but may prevent the condition among this population.
<b>Translocation</b>					
d’Ettorre et al [43]	Observational; n = 20	48 wk	+	+	Markers of immune activation (CD4 <sup>+</sup> CD38 <sup>+</sup> HLA-DR <sup>+</sup> , CD4 <sup>+</sup> CD38 <sup>+</sup> HLA-DR <sup>+</sup> , CD4 <sup>+</sup> CD38 <sup>+</sup> HLA-DR <sup>+</sup> ) and inflammation (hsCRP) decline from T0 to T1; markers of translocation (soluble [s]CD14, D-dimer) did not change significantly.
Falasca et al [40]	Observational; n = 30 men	4 wk	+	(+)	Some impact on inflammatory cytokine levels; statistically significant increase in TGF- $\beta$ ; increase in CD56 <sup>+</sup> NK cells (possibly associated with increase in IL4/IL-1 $\beta$ ratio). Statistically significant reduction in cystatin-C.
Gonzalez-Hernandez et al [3]	RCT; n = 20	16 wk	–	+	Reduction in 16S rDNA in synbiotic group ( $P = .048$ ). Increase in stool for beneficial bacteria and decline in <i>Clostridium</i> sp 5 in each arm, probiotic, prebiotic, synbiotic, placebo.
Gori et al [18]	n = 57 HIV <sup>+</sup> Each arm, n = 19;	12 wk	–	–	Activation markers: No effect (%CD8 <sup>+</sup> CD38 <sup>+</sup> DR <sup>+</sup> % CD4 <sup>+</sup> CD25 <sup>+</sup> FoxP3 <sup>+</sup> %CD14 <sup>+</sup> B7-H1*; %CD19 <sup>+</sup> B7-H1*). Increased NK cell effector/target ratios in 15 g group. No serious AEs, impact on liver/kidney function. Follow-up at 16 wk off treatment.
Schunter et al [42]	N = 33 HIV <sup>+</sup> women on ARV	4 wk	+	–	No effect on 16S rDNA, CRP, or TNF- $\alpha$ and $\gamma$ -IFN. Increase in % CD38-DR <sup>+</sup> PD1 <sup>+</sup> and decrease in CD38 <sup>+</sup>
Villar-García et al [26]	n = 44 HIV <sup>+</sup>	12 wk w/12 wk follow-up	+	–	LBP: Statistically significant decline in LBP 13.6% (n = 3) in the placebo group vs 50% (n = 11) in the probiotic group ( $P = .02$ ). IL-6: Reduction in per protocol analysis (n = 19 tx, n = 16 placebo) at 12 wk and persisting at 24 wk ( $P < .01$ ) $\beta_2$ M: Statistically significant reduction by ITT at week 24 vs placebo. However, this marker was higher at BL in treatment group ( $P = .02$ ). All other markers: No effect (including LPS, sCD14, hs-CRP, fibrinogen, TNF- $\alpha$ , ESR. Stable ARV, VL < 20 for at least 2 years.

Abbreviations: AE, adverse event; ARV antiretroviral; AZT, azidothymidine;  $\beta_2$ M, beta-2-microglobulin; BL, baseline; BMI, body mass index; BV, bacterial vaginosis; cfu, colony-forming units; CI, confidence intervals; CRP, C-reactive protein; ddl, didanosine; ESR, erythrocyte sedimentation rate; f/u, follow up; GI, gastrointestinal; HIV, human immunodeficiency virus; IL, interleukin; ITT, intent-to-treat; LBP, lipopolysaccharide binding protein; NK, natural killer; NS, not statistically significant; PP, per protocol; RCT, randomized controlled trials; rDNA, ribosomal deoxyribonucleic acid; S.b., *Saccharomyces boulardii*; SD, standard deviation; TGF, tumor growth factor; TNF, tumor necrosis factor; Tx, treatment; VL, viral load; WHO, World Health Organization.

A 25-week study among women also observed an average loss of 3 CD4 cells/ $\mu$ L with placebo versus an increase of 50 and 46 cells/ $\mu$ L with probiotics at 10 weeks, although the differences were not statistically significant. Mean or median baseline and end-of-study CD4 values were not provided. However, women with CD4 < 200 at baseline saw a greater mean increase in CD4

count of 93 cells/ $\mu$ L versus a mean decrease of 69 cells/ $\mu$ L among placebo recipients [29]. No benefit was seen in a 4-week study on CD4 count [36].

Some studies reported sporadic ARV use. Among those on zidovudine monotherapy, an apparent reduction was found in CD4 count in the probiotic arm, and the authors concluded that

“Because this trend continued after 2 week of washout it is not interpreted to be treatment related.” [37] An observational retrospective study over 3 years evaluated supplemented yogurt. Adjusting for length of time using ARV medication, probiotic users gained 0.17 cells/ $\mu\text{L}$  per day (or approximately 62 CD4/year); however, the nutritional content of the yogurt may also have had an effect [38].

Seven studies evaluated adults with HIV on ARV. In a 2-week crossover trial among 17 patients, no impact on CD4 was seen [35]. A 3-month study saw no change in absolute CD4 count; however, there was a significant increase in CD4 percentage compared with placebo (+2.8% vs -1.8%,  $P = .018$ ) [39]. An open-label study of 30 HIV<sup>+</sup> men observed an increase in CD4 over 4 weeks; however, this was not statistically significant [40]. A larger increase in those receiving glutamine and probiotics arm was significant compared with control [30]. A 3-period (30 days), crossover trial showed greater CD4 improvement in the micronutrient phase, whereas the addition of probiotics may have blunted the benefit [41]. A 4-week study using a synbiotic found no effect on CD4 count [42]. An open-label study among 20 HIV<sup>+</sup> adults on ARV over 48 weeks showed a median increase of 65 cells/ $\mu\text{L}$  [43].

In an open-label, pediatric study over 3 months, the probiotic group increased CD4 count 65 cells/ $\mu\text{L}$  compared with a loss of 88 cells/ $\mu\text{L}$  in the control in children >5 years, with a trend observed among children under 5: +22 CD4 versus placebo loss of 65 cells [23]. A 2-month pediatric study observed a 118 cell increase in mean CD4 count in children 2–12 years of age versus a loss of 42 cells/ $\text{mm}^3$  in the control arm [34].

We further assessed the studies based on their interventions and CD4 outcome to see whether any pattern of benefit, lack of benefit, or harm appeared. In reviewing the data from this perspective, all studies that used bacterial interventions such as *Bifidus* or *Lactobacilli* spp all reported moderate increases in CD4 counts. A larger increase was observed among those on a synbiotic (combination of prebiotics and probiotics); however, there were only 5 patients per arm [3]. No benefit for CD4 count was seen in one study of *S. boulardii*. Formal meta-analysis was precluded due to variability in use or not of ARV, populations (adult/pediatric) and variability in reporting CD4 data [3, 23, 29, 30, 38].

Overall, our analysis suggests a potential role for the use of probiotics in improving CD4 counts modestly. Longer-term studies of probiotics and synbiotics in the context of more advanced ARV therapy are warranted, as well as observational studies in communities where immediate ARV is not yet available.

#### **Probiotics Impact on Bacterial Vaginosis**

Bacterial vaginosis may increase risk of transmission or acquisition of HIV [44], increasing proinflammatory cytokines and disrupting mucosal barrier function [45]. We found 1 trial assessing the potential impact of probiotics. The only RCT,

among 65 HIV<sup>+</sup> women with BV defined as a Nugent score [44] of 4–10 over 6 months, showed no enhanced cure rate. However, the probiotic intervention may be prophylactic for BV [46].

#### **Probiotics/Prebiotics Effect on Human Immunodeficiency Virus-Associated Bacterial Translocation**

We found 6 studies that assessed the impact of probiotics or prebiotics on markers of translocation in HIV disease, 4 showing some effect and 2 showing none. A 16-week study of a synbiotic observed reductions in plasma bacterial deoxyribonucleic acid, and a median CD4 increase of 102 ( $P = .05$ ), along with a decline in interleukin (IL)-6 ( $P = .016$ ) [3]. A 4-week study with translocation as the primary endpoint found no effect on bacterial 16S ribosomal ribonucleic acid (RNA) concentration or soluble CD14 (sCD14) [42]. Another 4-week study using a yogurt drink observed an improvement in natural killer (NK) cell counts (CD56<sup>+</sup>) as well as modest reductions in messenger RNA cytokine levels of IL-1 $\beta$ , IL-10, IL-12, tumor growth factor- $\beta$ , along with the inflammatory marker cystatin-C [40]. However, a study of mix of probiotics over 48 weeks saw no effect on markers of translocation (sCD14), but it did see improvements in markers of activation and inflammatory markers (eg, high-sensitivity C-reactive protein) [43]. A prebiotic oligosaccharide mixture given over 12 weeks resulted in reductions in sCD14 and activated CD4<sup>+</sup>/CD25<sup>+</sup> cells along with increased NK cell activity [18, 47].

Among 44 HIV<sup>+</sup> individuals given *S. boulardii* over 4 weeks, LPS-binding protein (a marker of translocation) and IL-6 (a marker of inflammation) were statistically significantly decreased compared with placebo recipients. Other markers of inflammation, CD4 and CD8, were unaffected [26].

In summary, the data are inconclusive; however, there is a signal that prebiotics may have a modest impact on markers of translocation and/or markers of inflammation and immune activation. Studies assessing prebiotics versus synbiotics should be contemplated.

#### **Probiotics: Side Effects and Adverse Events**

The most serious potential adverse event from ingesting live organisms is sepsis. Numerous case reports of probiotic organisms causing bloodstream infection are reported, but no formal assessment has been made [15]. Snyderman [48] noted no evidence of an increase of bacteremia at a population level of use of probiotics and stated that more trials are needed. Several studies showed no risks associated with use among neonates [49–52], although caution exists for patients with a peripherally inserted central catheter line, environmentally acquired infections arising during severe immunosuppression, and use of prebiotic and synbiotic among those with pancreatitis [15, 53]. A large study observed increased mortality when using a multispecies probiotics preparation [54]; however, others suggest that probiotics may be safe when used [55].

We reviewed and combined RCTs in people with and without HIV where probiotics were administered and risk of sepsis arising from bacteremia or fungemia was explicitly assessed (Supplementary Table). We found 39 RCTs, where the total number of study participants is 9401, and the total number that received a probiotic is 5060. We found 0 events among these RCTs.

For the Bayesian fixed effects analysis, the resulting posterior distributions for the parameters are the Beta (9402, 1) and Beta (5061, 1) distributions for  $\pi$  and  $\rho$ , respectively. Using Monte Carlo integration (with 1 million samples from the posterior distribution), we approximate the posterior median of the NNH to be 7369 and the 95% posterior lower credible bound for the NNH to be 1689; that is, given the studies we found, there is a 95% chance that NNH is higher than 1688, and there is a 50% chance that the NNH is higher than 7369.

Mild adverse events were reported in a systematic review, including fewer events among treatment recipients than placebo [56]. Among HIV<sup>+</sup> adults, no unexpected adverse events (some flatulence and abdominal distension) were noted in medium- and higher-dose arms investigating a prebiotic [18].

In a review of 622 studies, 235 referred only to “well-tolerated” or other such nonspecific reference to side effects. The remaining 387 studies indicated no statistically significantly increased relative risk of overall number of adverse events. Among vulnerable populations they note: “Across studies, there was no indication that critically ill and high risk participants taking probiotics were more likely to experience adverse events than control participants with the same health status” [57].

## DISCUSSION

Firm conclusions are difficult due to variability in populations, interventions, and outcomes, and as a result, data synthesis on specific outcomes was precluded. Overall, probiotics appear to exert some positive influence on clinical symptoms, a moderate improvement on CD4 count, and limited effects on markers of translocation. It was disappointing to find that studies did not investigate the potential for vaginally or rectally applied probiotic suppositories as microbicides, even though such products are available on the market.

In HIV, diarrhea is caused by various infections and medications, eg, antibiotic therapy/prophylaxis, ARV therapy. Among HIV-negative populations, commensal organism supplements have a salutary effect on antibiotic-associated diarrhea [57], as well as inflammatory gut diseases and infections [15]. Mechanisms of action are not fully understood, but they may include interference with pathogen adhesion, growth and toxin release, modulation of immunity, and manipulation of host factors that reduce inflammation and encourage gut healing [2, 58].

There was some evidence that combinations of 2 or more strains were more efficacious than single strains in therapeutic and prophylactic effects on different forms of diarrhea, as some

review studies have suggested [59]. Studies investigating combinations of interventions may offer greater efficacy, eg, use of agents such as glutamine, *N*-acetylcysteine, micronutrients for managing diarrhea [60]. Studies that include micronutrients may optimize benefits, for example, in offsetting hyperlactatemia and mitochondrial toxicity associated with some ARV drugs [61] or improving gut architecture [62].

Antiretroviral therapy-treated individuals who fail to have an immunologic response (CD4 < 200) have been observed to have lower levels of *Lactobacilli*, with elevated levels of LPS and sCD14 [63], whereas other research underscores that increased inflammatory markers such as IL-6 and sCD14 are elevated compared with those achieving immunological restitution or to controls [64]. There is evidence for greater translocation among untreated individuals along with immunological perturbations (eg, increased activated CD38<sup>+</sup> and Ki67<sup>+</sup>) [65]. Few gut *Lactobacilli* may blunt ARV efficacy [66]. Most studies were too short to properly assess impact on immune function; however, some showed immunological benefit. Studies in macaque models underscore a potential for altering gut immunity through effects on Th17 cells [67]; however, a robust effect in improving Th17 cells in the gut was enhanced with infusion of IL-21 [68].

Probiotics show equivocal effects on markers of translocation. Although the impact of probiotics on BV was not strong, there is some evidence that BV may be prevented [69, 70], possibly reducing risk of HIV transmission.

As for the most feared risk, fungemia or bacteremia, our NNH should provide reassurance, whether one adopts the point estimate (7634) or, more conservatively, the lower bound (1689). Indeed, even the point estimate is conservative because the many studies excluded for lack of explicit assessment of sepsis most likely would have reported such an adverse event. The observed rate is far lower than to the risks of some commonly prescribed conventional medications. For example, widely used proton pump inhibitors increase the risk of *C difficile* infection, with a NNH ranging from 28 of those admitted to hospital using antibiotics to 899 among community patients [71]. Longer-term and community-based trials should provide more robust data.

### Strengths

This systematic review evaluates the use of probiotics for the full range of outcomes in HIV disease. We developed a model for the assessment of sepsis risk in the face of a “zero numerator” challenge, helping to quantify potential risk.

### Limitations

Many studies were of short duration and comprised small numbers of patients and variability in the nature of the interventions used and outcomes assessed. We deemed it inappropriate to undertake formal meta-analyses of prespecified outcomes, except for risk of sepsis. The methodological quality of several of the studies was poor (Table 2).

## CONCLUSIONS

In this study, we discovered the following key results: the risk of sepsis is low; the best balance of microbial strains to use to optimize outcomes has not yet been identified, and such combinations may be specific to indications, populations, and genders; there may be potential benefit for CD4 count, recurrence, or management of BV and diarrhea; and there is an uncertain effect on translocation, BV treatment.

Future studies should focus on restoration of optimal gut, vaginal, or rectal microbiomes. There is intense and growing interest in characterizing the microbiome, including which gut ecologies are more optimal for health [72, 73]. Longer-term studies should explore using a community-relevant mix of bacteria and/or fungi for outcomes such as diarrhea and CD4 count. Studies among women to assess effects on vaginal, gastrointestinal, and microbicidal effects are warranted, as well as the use of *Lactobacilli* in suppositories. Species of *Lactobacilli* in combination with other genera may have clinically meaningful effects among those with poor immunological response despite ARV; these subsets and impact on inflammatory markers deserve further scrutiny. Such studies with immunological outcomes (CD4, activation markers) require longer duration, particularly in the context of ARV use. Such studies are being contemplated [74]. Studies of *S. boulardii* for noninfection-associated diarrhea are warranted.

Given the paucity of evidence for adverse events, low cost, and potential for economic value to people living in poverty [2, 12], the use of probiotics seems practical and feasible. Restoration of gut flora to a more healthful ecology may have several important clinical benefits particularly in conjunction with improved nutrition and access to micronutrient supplementation [75].

## Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases online* (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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