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Fecal Microbiota Transplantation for People Living with Human Immunodeficiency Virus: A Scoping Review

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Abstract

The aim of this scoping review was to determine the characteristics of studies evaluating fecal microbiota transplantation (FMT), as well as its effects and safety as a therapeutic intervention for people living with human immunodeficiency virus (HIV). We conducted a scoping review following the methodology of the Joanna Briggs Institute. We searched the following databases: PubMed, Web of Science, Scopus, Embase, Cochrane Library, and Medline until September 19, 2021. Studies that used FMT in people living with HIV and explored its effects on the health of these people were included. Two randomized and 2 uncontrolled clinical trials with a total of 55 participants were included. Participants were well-controlled HIV-infected people. Regarding microbiota changes, three studies found significant post-FMT increases in *Fusobacterium*, *Prevotella*, α-diversity, Chao index, and/or Shannon index, and/or decreases in *Bacteroides*. Regarding markers of intestinal damage, one study found a decrease in intestinal fatty acid binding protein post-FMT, and another study found an increase in zonulin. Other outcomes evaluated by the studies were as follows: markers of immune and inflammatory activation, markers of immunocompetence ($CD4^+$, and $CD8^+$ T lymphocytes), and HIV viral load; however, none showed significant changes. Clinical outcomes were not evaluated by these studies. Regarding the safety of FMT, only mild adverse events were appreciated. No serious adverse event was reported. The clinical evidence for FMT in people living with HIV is sparse. FMT appears to have good tolerability and, no serious adverse event has been reported so far. Further clinical trials and evaluation of clinically important biomedical outcomes for FMT in people living with HIV are needed.

Keywords: HIV, fecal microbiota transplantation, intestinal microbiome

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Introduction

HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection causes a chronic inflammatory state, which is characterized by a high turnover and activation of T and B lymphocytes with increased proinflammatory mediators.[1] One of the factors contributing to this inflammatory state is the change in the composition of the intestinal microbiota characterized by a decrease in symbiotic bacteria and an increase in pathobiont bacteria.[2] In addition, there is a depletion of $CD4^+$ T lymphocytes at the intestinal barrier, with destruction of tight junctions, decreased IgA, dysfunctional macrophages, and death of enterocytes, all of which facilitate the translocation of pathogens[3] and microbial products from the permeable intestinal barrier into the circulatory system. As a result, there is production of proinflammatory cytokines such as interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF), interferon (IFN)a, and IFNb.[4]

Certain interventions, such as dietary modification with the use of prebiotics that would restore intestinal bacteria, inhibition of microbial enzymes that exacerbate intestinal inflammation, targeted elimination of microbiota flora through phages, and fecal microbiota transplantation (FMT), have been proposed as potential therapeutic measures to reverse these alterations.[5] FMT is the transfer of stool from healthy donors with the aim of normalizing the composition and function of intestinal microbiota.[6] Good tolerability and safety have been reported with this strategy, as well as an increase in microbial diversity and improvement of intestinal inflammatory markers in people living with HIV.[7] However, great variability has been identified in the outcomes evaluated by the studies, so a scoping review approach was chosen to identify the available evidence on this topic.[8]

This scoping review aims to determine the characteristics of studies evaluating FMT, as well as its effects and safety as a therapeutic intervention for people living with HIV.

Methods

We performed a scoping review following the guidelines of the Preferred Reporting Items for Systematic and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) of 2020[9] and the methodology described by the Joanna Briggs Institute.[10] The study protocol was registered on the Figshare platform (FMT for people with HIV: a scoping review protocol).

Eligibility criteria

We have included clinical trials and observational studies that reported health-related outcomes described post-FMT in people living with HIV. Case reports, editorials, commentaries, reviews, and studies not available in full text were excluded.

Literature search

The following databases were searched for articles: (1) PubMed, (2) Web of Science/Core collection, (3) Scopus, (4) Embase, (5) Cochrane Library, and (6) Web of Science/MEDLINE. The search was conducted on September 19, 2021. There was no restriction regarding language or date of publication. Search terms were grouped into two categories: HIV/AIDS and fecal transplantation. The full search can be found in Supplementary Table S1.

Study selection

Duplicate items were manually removed with EndNote software.[11] Subsequently, the studies were imported into the Rayyan software.[12] Two authors (B.C.-C. and I.P.-L.) independently reviewed the titles and abstracts of the results to identify potentially relevant studies for inclusion. These studies were full-text reviewed independently by two different authors (K.F.-L. and A.G.-U.). Any disagreement in selection was discussed with another author (D.R.S.-M.) and resolved by consensus. In addition, the reference list of all included studies was reviewed to complement the search.

Data charting

An extraction sheet was designed in Microsoft Excel and the data of interest were obtained independently by the authors (D.F.-G. and J.F.-M.). Discrepancies were resolved with two different authors (D.R.S.-M. and S.M.-R.). The following variables were extracted from each study: first author, year of publication, country, study design, population characteristics (age, sex, and number of participants), follow-up time, HIV status of the patients, donor features, details of FMT, outcomes assessed by the studies, and adverse events. Regarding outcomes, we only included those that gave some statistical measure (e.g., *p* value) to know whether the change was significant or not.

Synthesis of results

A descriptive synthesis of the results of included studies was performed. We made tables and figures to summarize the characteristics, outcomes, and adverse events reported by the studies.

Results

Study characteristics

The systematic search identified 274 studies through database and registers after removing duplicates. We identified 193 studies from references of included articles. After screening, we obtained 15 studies (12 from database and registers, and 3 from references), which were reviewed in full text to assess their eligibility. Finally, four studies were included in the review (Fig. 1). The reasons for the exclusion of full-text reviewed articles are detailed in Supplementary Table S2. The studies were clinical trials, two of which were randomized[13,14] and two uncontrolled.[15,16] The follow-up time for these studies was at least 24 weeks. There were 55 participants in total, more than 85% were men. Their age ranged from 28 to 72 years. The participants were well-controlled HIV-infected adult people on highly active antiretroviral therapy (HAART).[13–16]

One study included patients during at least 48 weeks on stable HAART[13] and another during at least 24 weeks.[15] Almost all participants continued with HAART during follow-up. Two studies included only men who have sex with men (MSM)[15,16] and another included a high proportion of MSM.[13] In Serrano-Villar *et al.*'s [13] study, six participants received antibiotics in the 14 weeks before the intervention; and in SahBandar *et al.*'s study,[16] nine participants received antibiotics in the 5 days before the intervention. Two studies administered FMT orally with multiple doses[13,15] and two

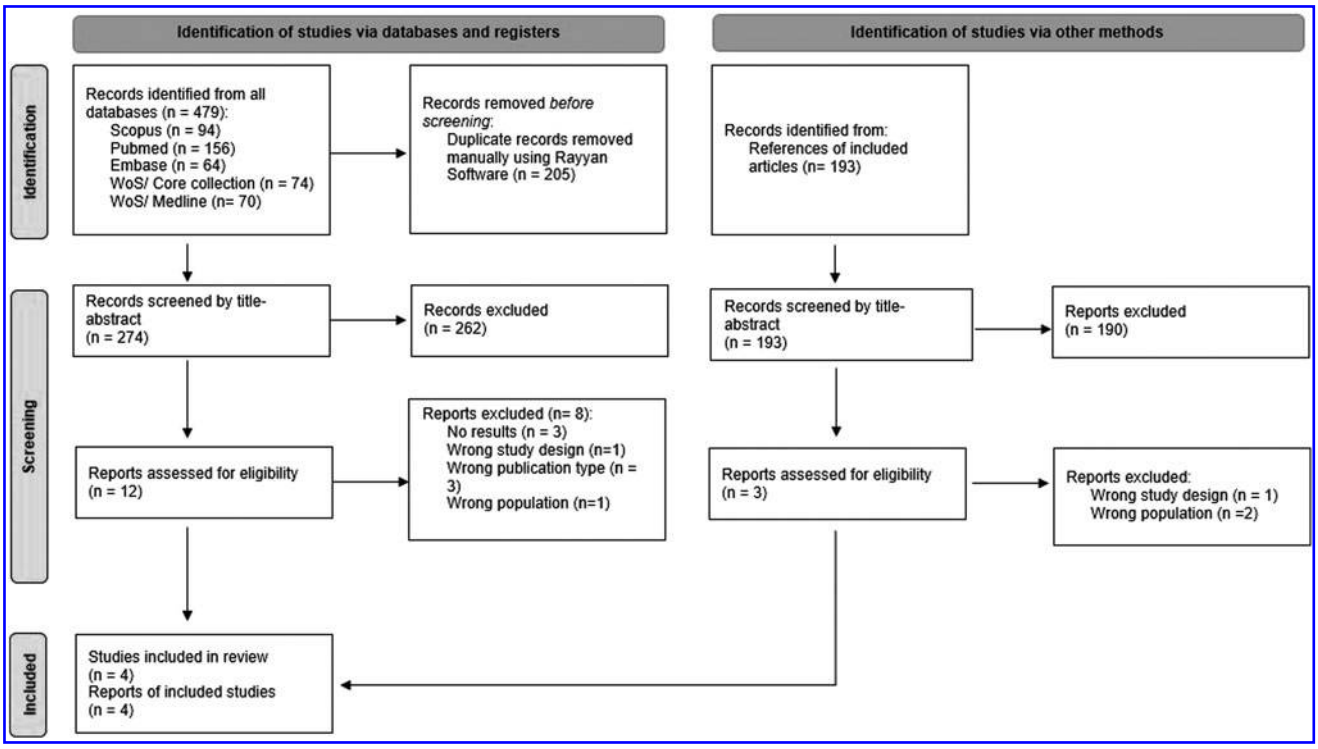


FIG. 1. Flow diagram summarizing the process of literature search and selection.

studies administered FMT by colonoscopy.[14,16] Donors were healthy adults with high *Bacteroides* concentrations (Table 1).

Clinical outcomes and markers of immunocompetence

None of the studies evaluated clinical outcomes. Regarding immunocompetence markers, three studies evaluated $CD4^+$ and $CD8^+$ T lymphocytes, and $CD4^+/CD8^+$ ratio.[13–15] Only Utay *et al.* measured HIV RNA viral load.[15] No significant change in these outcomes was found.

Inflammatory and immune activation markers

In terms of macrophage activation markers, sCD14 level and sCD163 were evaluated by three and two studies, respectively.[13,15] Two studies analyzed IFN-γ levels.[15,16] Other assessed markers were as follows: IL levels, TNF-related weak inducer of apoptosis (TWEAK), matrix metallopeptidase 1, plasma kynurenine to tryptophan ratio, D-dimer, IFN-γ-induced protein 10, and soluble tumor necrosis factor receptor type II.[15] None of the studies found significant changes in markers of inflammation and immune activation.

Microbiota modification

The studies evaluated the microbiota by 16s rRNA sequencing, except for Utay *et al.*'s study, which did not provide details. The following bacteria were evaluated: *Fusobacterium, Faecalibacterium*, Rikenellaceae, *Prevotella,* Erysipelotrichaceae, and *Bacteroides*. One study found a significant increase in the population of *Fusobacterium,*[15] and another found a significant increase in the population of *Prevotella* and a significant decrease in *Bacteroides.*[14] In addition, the α-diversity was evaluated by three studies,[13–15] finding a significant increase in only one of them.[13] Furthermore, Serrano-Villar *et al.* found a significant increase in Chao index and Shannon index.[13]

Bacterial translocation and gut damage markers

The selected studies evaluated markers of intestinal damage such as intestinal fatty acid binding protein (IFABP),[13,15] zonulin,[13,15] and flagellin.[15] Serrano-Villar *et al.* found a significant decrease in IFABP levels,[13] and Utay *et al.* found a significant increase in zonulin levels.[15] Regarding markers of bacterial translocation such as lipopolysaccharide binding protein and lipoteichoic acid, no significant change was found.[15] All outcomes are detailed in Figure 2.

Adverse events

Adverse events reported in the groups receiving FMT were nausea, abdominal pain, bloating, flatulence, and diarrhea. SahBandar *et al.*'s study did not report adverse events. There was no serious adverse event developed by the participants in any of the studies (Table 2).

Discussion

Main results

In this scoping review, we included four clinical trials (two randomized and two uncontrolled) that evaluated FMT in people living with HIV. The outcomes assessed by these studies were markers of immunocompetence, HIV viral load, markers of inflammatory and immune activation, microbiota modification and bacterial translocation, and markers of intestinal damage. Some studies reported significant changes in

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Table 1. Characteristics of Included Studies Evaluating Fecal Microbiota Transplantation in People Living with Human Immunodeficiency Virus ($N=4$)

Author (year)	*Country*	*Design*	*Sample size*	*% Male sex*	*Age ± SD, years*	*Follow-up, weeks*	*HIV status*	*Donor details*	*Fecal microbiota transplantation details*
Serrano-Villar *et al.* (2021)[13]	Spain	Randomized clinical trial	29	89.7	47.0 ± 11.1	0, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, and 48	69% MSM on stable triple ART with plasma HIV RNA <37 copies/mL during at least 48 weeks and a CD4/CD8 ratio <1	Upper quartile of abundance and butyrate concentrations of the fecal *Bacteroides* and *Faecalibacterium* genera, and in the lower quartile of *Prevotella* abundance	Oral administration of capsules vs. placebo. Induction dose with 10 capsules (single dose). And maintenance dose weekly with 5 capsules for 7 weeks.
Utay *et al.* (2020)[15]	United States	Uncontrolled clinical trial	6	100	39.0 ± 22.9	0, 6, and 26	MSM, HIV positive, on continuous triple ART for ≥24 weeks, with $CD4^+$ T cell count >350 cells/mm^3, HIV RNA levels <20 copies/mL for ≥12 weeks, and absolute neutrophil count ≥1,000 cells/mm^3	Healthy men 56 to 68 years old with BMI <30 kg/m^2 and no personal or family history of disease suspected to be transmitted by the microbiome	150 g of stool (lyophilized to ~2.25 g) from 1 of 3 donors, weekly for 6 weeks. Participants fasted, except for water, for 8 h before the intervention. They took the product under supervision and were monitored for 1.5 h after ingestion.

(*continued*)

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Table 1. (Continued)

Author (year)	*Country*	*Design*	*Sample size*	*% Male sex*	*Age ± SD, years*	*Follow-up, weeks*	*HIV status*	*Donor details*	*Fecal microbiota transplantation details*
SahBandar *et al.* (2020)[16]	United States	Uncontrolled clinical trial	12	100	54.8 ± 12.9	–4, –2, 0, 1, 2, 4, 8, and 24	MSM, HIV positive, on stable combination ART, with viral load undetectable, CD4 count >250 cell/mm^3	Low in *Proteobacteria* and high in *Bacteroidetes*.	Participants underwent a standard bowel purge the day before the intervention and the 250 mL fecal suspension was administered through colonoscopy into the ileum, cecum, and ascending colon.
Vujkovic-Cvijin *et al.* (2017)[14]	United States	Randomized clinical trial	8	87.5	56.3 ± 13.7	–4, –2, 0, 1, 2, 4, 8, and 24	Participants on continuous ART with full viral load suppression. CD4 > 250 cell/mm^3	Low in *Proteobacteria* and high in *Bacteroidetes*.	Participants underwent a standard bowel purge the day before the intervention and the 250 mL fecal suspension was administered through colonoscopy into the ileum, cecum, and ascending colon.

ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; MSM, men who have sex with men; SD, standard deviation.

Author (Year)	Clinical outcomes		Immune competence markers			Viral load	Inflammatory and immune activation markers										Microbiota modification									Bacterial Translocation and Gut damage				
	Infections	Others	CD4	CD8	CD4/CD8	HIV RNA levels	Macrophage activation		IFNγ	Interleukins	MMP-1	Kyn/Trp	TWEAK	Others			Fusobacterium	Faecalibacterium	Rikenellaceae	Prevotella	Erysipelotrichaceae	Bacteroides	α-diversity	Chao-index	Shannon-index	IFABP	LBP	Lipoteichoic acid	Flagellin	Zonulin
							sCD14	sCD163						D-dimer	sTNFr II	IP-10															
Serrano-Villar -2021			x	x	x		x	x						x	x	x		x			x		x	x	x	x	x		x	x
Utay -2020			x	x	x	x	x	x	x	x	x		x		x		x					x	x			x			x	x
SahBandar-2020									x								x													
Vujkovic-Cvijin-2017			x	x	x		x					x						x	x	x	x	x	x							

Underlined values: statistically significant changes, IFNγ: Gamma interferon, MMP-1: Matrix metallopeptidase 1, Kyn-Trp: Kynurenine to tryptophan, TWEAK: TNF-related weak inducer of apoptosis, sTNFr II: Soluble tumor necrosis factor receptor type II, IP-10: Interferon gamma-induced protein 10, IFABP: Intestinal fatty-acid binding protein, LBP: Lipopolysaccharide-binding protein.

FIG. 2. Outcomes evaluated in studies evaluating fecal microbiota transplantation in people with HIV ($n=4$). HIV, human immunodeficiency virus.

the composition of intestinal microbiota and markers of intestinal damage. However, no study evaluated clinical outcomes. Regarding safety and tolerability, there was no serious adverse event, but mild side effects such as bloating and mild abdominal pain, flatulence, nausea, and diarrhea were reported.

Characteristics of the studies

The four trials included people living with HIV with different clinical and immunological characteristics, and three studies included a high proportion of MSM.[13,15,16] The importance of considering this characteristic in people living with HIV laid in the fact that sexual preferences could generate alterations in the microbiota, increasing the presence of *Prevotella* and favoring alpha and beta diversity.[17–19]

Regarding the method of administration of FMT, we observed that two studies used the oral route (ingestion of the product or capsules) and two used colonoscopy. These routes have been previously considered in previous studies that evaluated the effect of FMT on *Clostridium difficile* infection, with a higher cure rate observed in those who used colonoscopy, followed by capsule and enema, with the lowest cure rates observed with nasogastric tube administration[20]; this could suggest that passage through the upper digestive tract could interfere with the effect of FMT.

Similarly, administration of FMT as an intervention to seek clinical remission of ulcerative colitis was more effective when colonoscopy was used compared to the oral route.[21] The role of bowel purging before colonoscopy has not been evaluated; however, there would be no theoretical support for thinking that it could modify the microbiome of patients with HIV.[14–16]

On the other hand, the volume and frequency of FMT administration were not equal for studies that evaluated the effect of oral FMT, whereas for studies using colonoscopy, the volume and segments of the colon where it was administered were standard. In previous studies on the effectiveness of FMT for the cure of *C. difficile* infection, it has been observed that dose heterogeneity does not show linearity or

Table 2. Adverse Event Frequency of Fecal Microbiota Transplantation in People with Human Immunodeficiency Virus ($N=4$)

Author (year)	*Group*	*Nausea*	*Abdominal pain*	*Abdominal distension*	*Flatulence*	*Diarrhea*	*Serious adverse events*
Serrano-Villar *et al.* (2021)[13]	Intervention group ($n=14$)	0	0	35.7%	35.7%	35.7%	0
	Control group ($n=15$)	0	0	0	6.7%	0	0
Utay *et al.* (2020)[15]	Intervention group ($n=6$)	16.7%	16.7%	16.7%	0	0	0
SahBandar *et al.* (2020)[16]	Intervention group ($n=12$)	Not reported					
Vujkovic-Cvijin *et al.* (2017)[14]	Intervention group ($n=6$)	0	0	0	0	0	0
	Control group ($n=2$)	0	0	0	0	0	0

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association with a higher cure rate.[22] Similarly, Wang *et al.*[23] evidenced that an induction dose may not contribute significantly to treatment success. On the other hand, a systematic review of 37 studies evaluating FMT in patients with recurrent *C. difficile* infection found that repeated doses of FMT were associated with greater clinical success.[22]

In addition, a systematic review of four interventional studies, which evaluated the effect of FMT as salvage therapy in patients with ulcerative colitis, mentioned that the treatment provided clinical remission after 8 weeks of multiple administrations of FMT.[24]

In people living with HIV, there is even greater uncertainty about the dosing, route of administration, and follow-up time of TMF. Clearly, more studies are needed to determine these aspects. With respect to uncontrolled studies, it is not possible to conclude with certainty that changes in outcomes were due to FMT, given the absence of a control group. In addition, the randomized control trials and uncontrolled studies had small sample sizes.

Changes in immune response

It has been proposed that the FMT or modification of the microbiome is beneficial for the immune system, influencing the response of T cells and reversal of dysbiosis in people with HIV and gastrointestinal tract diseases.[25–29] In this review, we found that FMT did not modify $CD4^+$, $CD8^+$ levels, $CD4^+/CD8^+$ ratio, and inflammatory markers.[13–15] It is possible that due to the small sample size of the studies, no benefit was found. Studies with a larger number of participants and with a longer follow-up time are needed to evaluate these important outcomes.

Changes in the microbiota

Studies have demonstrated that the microbiota of people living with HIV suffers an alteration in its composition, which causes dysbiosis,[30] leading to an increase in bacteria that produce proinflammatory substances (Erysipelotrichaceae, Enterobacteriaceae, *Fusobacteria*, and *Prevotella*) and a decrease in anti-inflammatory bacteria (*Bacteroides* and Rikenellaceae). These events trigger the dysregulation of different subsets of T cells, generating inflammation and prolonged damage to the organism.[5,31–33] Therefore, controlling the colonization of bacterial colonies in the microbiota may be used as a therapeutic strategy aiming to restore the homeostasis in people living with HIV.

In this review, the study conducted by SahBandar *et al.* demonstrated the persistence of *Fusobacterium* post-FMT. Utay *et al.* found an increase in intestinal *Fusobacterium* colonization, and Vujkovic-Cvijin *et al.* observed an increase in *Prevotella* and a decrease in *Bacteroides* during follow-up, these changes being statistically significant. This paradoxical finding suggests that FMT may contribute to the increased dysregulation between proinflammatory and anti-inflammatory bacteria.

On the other hand, Utay *et al.*'s study[15] showed an increase in the variety and abundance of microorganisms in the microbiota (alpha diversity) during the first 6 weeks among people with low diversity. Meanwhile, Serrano-Villar *et al.*'s[13] study revealed an increase in alpha diversity,[34] as well as in their richness and uniformity (Shannon index). They also noted an elevation in the richness of microorganisms that differ between each patient (Chao index).[35]

Regarding the composition of the donor's microbiota, Serrano-Villar *et al.*'s study showed that there was a more pronounced effect on the alpha diversity of the participants who were assigned to a donor whose main characteristic was a greater abundance of the family Ruminococcaceae compared to other donors. However, this could not be conclusive because three out of five recipients of the donor had received antibiotics before the FMT intervention. This could have influenced the response after the intervention. Further studies should include donors with a microbiome with a predominance of microorganisms with anti-inflammatory effects.

Although the microbiota is not an absolute determinant associated with health problems, it is a mediating factor that could influence patient health, since a functional microbiota could reduce persistent and chronic inflammation during HIV disease.[36,37] Previous studies have shown that, in response to deregulation in the composition of the microbiota, it could generate health problems due to the production of immunomodulatory substances, which could be involved in inflammatory bowel diseases and colorectal cancer, among others.[38] On the other hand, it could generate less immune activation, being more prone to infections by opportunistic pathogen.[37,39]

Markers of intestinal damage

People living with HIV have local inflammatory response, which is measured indirectly by biomarkers intestinal damage (e.g., IFABP).[40–42] In this review, we found inconsistent results regarding whether FMT increases or decreases this intestinal damage, as measured by biomarkers. The study conducted by Serrano-Villar *et al.* found a decrease in IFABP post-FMT, indicating a decrease in intestinal damage, while Utay *et al.* observed an elevated concentration of zonulin, a marker of intestinal permeability, which would reflect a turnover of healthy intestinal epithelial.[43] An increase in the levels of zonulin has been associated with lower mortality in people living with HIV.[40]

Adverse events

Regarding tolerability and adverse effects of FMT, studies reported mild adverse events after both oral and colonoscopy procedures. In this regard, 7% of patients undergoing a colonoscopy could develop complications highlighting the bleeding and perforation.[44] This could imply a higher risk of complications compared to the oral route. Similarly, in a meta-analysis of adverse events of FMT, 4 out of 10 patients who received FMT for the management of different pathologies most frequently experienced bloating, abdominal pain, nausea, vomiting, and diarrhea, with *C. difficile* infection being the most serious adverse effect of FMT in immunocompetent individuals. This latter event was very infrequent.[45] Therefore, intervention in immunosuppressed patients should be performed under continuous supervision and monitoring.

Limitations of the studies

The main limitation of the included studies was the small sample size (with a minimum of 6 and a maximum of 29 participants included). Furthermore, they were heterogeneous in terms of characteristics of participants and donors,

intervention, follow-up time, and parameters to assess the efficacy of FMT. Another important limitation was that two studies had no comparator group. Finally, no study evaluated clinical outcomes.

Implications and recommendations

From this scoping review, we provide a general approach to be considered before developing future studies about FMT in people living with HIV. We recommend that the research conducted to evaluate FMT incorporates standardization of the intervention according to the methodologies used in the included studies (sample collection from specific donors, sample meeting microbiological criteria, and administration under protocol if colonoscopy is used). In addition, adequate follow-up should be considered to evaluate the results of the intervention with the following parameters: immune markers (CD4 level, CD8, and CD4/CD8 ratio), HIV viral load, inflammatory markers, immune activation markers, and changes in the microbiota, as well as clinical outcomes (opportunistic infections, mortality, etc.).

Limitations and strengths

Our scoping review has some limitations that should be taken into account. The primary evidence was sparse. We did not formally assess the methodological quality of studies that evaluated FMT. In addition, by including only published studies, there is the possibility of incurring in publication bias. Despite these limitations, this is the first scoping review that provides an overview of the literature in this area. The review was based on the methodology recommended by the JBI and PRISMA guidelines.[9,10] Finally, we believe that our results may contribute to build up the scientific evidence about FMT in people living with HIV. The methods of the review and search strategies may serve to guide the development of a protocol for future systematic reviews on this topic.

Conclusion

Sparse evidence is available on the benefits and potential risks of FMT in people living with HIV. With the available data, we cannot recommend its use in clinical practice. More clinical trials are needed to assess the efficacy and safety of this intervention.

Authors' Contributions

B.C.-C. and D.F.-G. conceived the study. All the authors wrote the article. D.R.S.-M., J.A.G.-Z., and J.H.-M. critically reviewed the article. All authors contributed to and approved the final version.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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