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Changes in the Gut Microbiome of people with HIV, clinical relevance and therapeutic avenues

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HIV infection is known to damage the gut lining early in the course of disease, largely because the virus rapidly depletes CD4⁺ T cells in the gastrointestinal tract. With effective antiretroviral therapy (ART), immune activation and inflammation are reduced but are generally not normalized.

One of the factors known to contribute to this state of persistent immune activation is that even under ART, bacterial products continue to leak from the gut into the bloodstream, a process called microbial translocation.

In an effort to understand how the gut microbiome and microbial translocation may contribute to incomplete immune recovery, many studies have examined the gut microbiome in people with HIV (PWH).

While different studies often revealed links to different genera, a common and coherent aspect is that irrespective of ART, distinct genera within the class of *Gammaproteobacteria* tend to be enriched in PWH.

Whether alterations in the composition of the gut microbiome, i.e. dysbiosis, is a direct consequence of HIV infection remains debated. Causality aside, the fact remains that PWH have been reported by a vast number of studies to have an altered composition of their gut microbiome. Blood concentrations of IFABP, LPS and sCD14 are commonly assessed measures that can help gauge microbial translocation. This overview provides details on what is known to date about how an altered composition of the gut microbiome may contribute to chronic immune activation and inflammation.

In addition, this report outlines some of the most studied therapeutics approaches that have been considered to normalize inflammation through the restructuring of the gut microbiome in adults living with HIV. So far, the effect of Probiotics in adults have not been consistent. Therapeutic strategies such as FMT in PWH appear safe and show promise but remain in early stages as long-term benefits are unclear.

Dietary changes and exercise are a mechanistic plausible avenue and remain underutilized in clinical trials but have shown preliminary beneficial effects.

The human microbiome encompasses communities of bacteria, viruses and eukaryotes that resides at different sites of the human body. The precise species composition and microbial abundance varies across body sites [1], with the gut holding the most diverse and most abundant share of the human microbiome. In the healthy gut, *Actinobacteria, Bacteroidetes, Firmicutes*, *Proteobacteria* and *Verrucomicrobia* represent the five most abundant phyla; and *Firmicutes* and *Bacteroidetes* account for the largest fraction of the gut bacteria [2].

Among their many functions, gut bacteria support the metabolism of complex dietary carbohydrates, with the degradation of dietary fibers resulting in the production of organic acids, gases and short-chain fatty acids (SFCAs) [3]. Further properties of gut bacteria involve maintaining the gut barrier function, supporting mucus secretion and preventing colonization by dysbiotic bacteria, thus contributing to homeostasis and immunity through a healthy gut. Numerous studies have reported changes in the composition of the gut microbiome of untreated people with HIV as well as in those receiving antiretroviral therapy (ART). Early during the course of the disease, HIV infection is paired with the damage of the gut lining, largely due to the depletion of CD4⁺ T cells in the gastrointestinal tract. This damage of the gut lining allows bacterial products to leak from the gut into the bloodstream - a process called microbial translocation [4].

Some of the more commonly measured indicators of microbial translocation in the blood include intestinal fatty-acid binding protein (IFABP), a marker of intestinal barrier dysfunction that is normally present in epithelial cells of the small intestine but is released into the circulation upon damage of the gut mucosa [5].

Furthermore, soluble CD14 (sCD14) is shed by activated monocytes in response to bacterial lipopolysaccharide (LPS) [6] and higher blood levels of sCD14 may reflect higher exposure to LPS. As a result of microbial translocation, more microbial products reach systemic sites in PWH even under ART, where they can activate circulating immune cells and thus contribute to systemic inflammation. In line with this, many reports have demonstrated that despite ART, PWH do not have normalized levels of inflammation and immune markers as seen with high serum or plasma levels of various soluble markers (e.g. IL-6, sTNFR1) that together with indices of microbial translocation associate with frailty [7].

Understanding exactly how the gut microbiome changes during HIV infection has for long been an area of high interest. Following the phylogenetic classification, reports have typically assessed broad composition at the phylum level down to a more granular analysis at the genus level. At the phylum level, *Proteobacteria* were reported to have a higher abundance in people with HIV on or off ART [8-10] whereas others reported a high ratio of *Prevotella* to *Bacteroides*, two genera of the phylum of *Bacteroidetes* [11, 12]. Despite the lack of consistent findings on the overall measures of diversity or phyla distribution, more studies could link distinct microbial genera to changes in the gut microbiome of PWH. Although different studies have been highlighting different genera – reminiscent of the heterogeneity of the microbiome between persons, sex, ethnicities and locations – a general observation could be made that in ART-treated PHW, some bacteria groups are reduced (e.g. *Lachnospiraceae*, *Faecalibacterium* and *Eggerthellaceae*) whereas others are enriched (e.g. *Enterobacteriaceae, Negativicutes, Peptoniphilus*, *Anaerococcus* and *Finegoldia)* [13]. Similar to ART-treated HIV infection, the families *Gammaproteobacteria* and *Negativicutes* tend to be enriched in the gut during untreated HIV infection whereas several genera of the *Lachnospiraceae* family are depleted. Considering the multitude of factors that have been shown to influence the composition of the gut microbiome, be it age [14], diet [15], sex hormones [16], lifestyle [17], ethnicity [18], geography [19] and host polymorphism [20]; an important aspect of microbiome evaluation is not necessarily which species, genus, family or phyla are more or less abundant but what are the functional properties of the microbes that are either enriched of lost. As such, the overall assessment of the properties of enriched and depleted groups suggests that in ART-treated HIV infection, there is an enrichment of gut bacteria with strong pro-inflammatory capability at the expense of those with anti-inflammatory/regulatory effects. For instance, *Faecalibacterium* (*Firmicutes* phylum) is known to have anti-inflammatory effects [21], is an important producer of the metabolite butyrate that reduces gut epithelial permeability by regulating tight junction proteins [22], and the relative abundance of *Faecalibacterium* was shown to inversely correlate with plasma sCD14 [10, 23, 24] and IFABP [12] during treated HIV infection. In contrast, *Gammaproteobacteria* are typically associated with intestinal inflammation, are known to preferentially translocate from the gut to systemic sites [25, 26], and facultative anaerobic bacteria such as the family *Enterobacteriaceae* (*Proteobacteria* phylum, *Gammaproteobacteria* family) have been proposed to have a selective advantage driving their expansion in the gut upon increased oxygen availability [27]. Moreover, *Gammaproteobacteria* exclusively carry the gene encoding for the hexa-acetylated form of LPS that is by two orders of magnitude the most potent agonist of the LPS receptor TLR-4 [28]. In treated HIV infection, the relative abundance of *Enterobacteriaceae* was shown to positively correlate with plasma levels of sCD14 [9]. Further supporting the central role of bacterial LPS in persistent inflammation in PWH, *Negativicutes*, that are also enriched in treated HIV-infection, are unique among *Firmicutes* in that they possess an outer membrane containing LPS [29]. The overall increase of pro-inflammatory bacteria at the expense of those with anti-inflammatory/regulatory function in the gut of PWH has also been proposed to be predictive of cancer risk in PWH irrespective of malignancy types [30], underlining long-term consequences of microbial translocation.

Of the few studies with PWH that have explored the translocated microbiome in the blood, thus fragments of microbial origin that may not form a whole organism but are sufficient to trigger immune responses, constituent derived from *Gammaproteobacteria* [31] or *Betaproteobacteria* [32] were enriched in the blood and associated with inflammation-related proteins in the plasma. Of note, while blood levels of sCD14 and LPS have been linked in many studies to a higher burden of inflammation-related non-communicable diseases such as cardiovascular disease or liver disease, both sCD14 and LPS did not always show an association across studies when other measures such as bacterial metabolites (e.g. SCFA) or markers for enterocyte damage (e.g IFABP) did [33]. This underlines the necessity and advantage of measuring multiple indicators of microbial translocation in the blood in order to understand its effects and potential implications.

Intriguingly, the question of whether HIV infection causes a dysbiosis of the gut microbiome has been controversial. A microbiome study of PWH that controlled for risk factors associated with HIV acquisition, determined that microbiome dysbiosis is predicted by the nadir CD4 $^{+}$ T-cell count [34], concluding that a higher degree of immune impairment, not HIV infection per se, is what contributes to dysbiosis. On the other hand, even HIV elite controllers, who are known to naturally control virus replication and retain high CD4 T cell counts for a prolonged period of time, have also been reported to have an altered composition of the gut microbiome [35, 36]. Thus, much remains to be clarified about the exact nature, cause and mechanisms of the changes in the gut microbiome of PWH and whether these, are at all a direct consequence of the viral infection. Nonetheless, the phenomenon of microbial translocation and its involvement in chronic immune activation and inflammation in PWH is undisputed **(Figure 1).** Therefore, there is a general interest in the field of HIV research to identify methods that may restore a balance in the gut microbiome and thus help limit inflammation and immune activation in PWH.

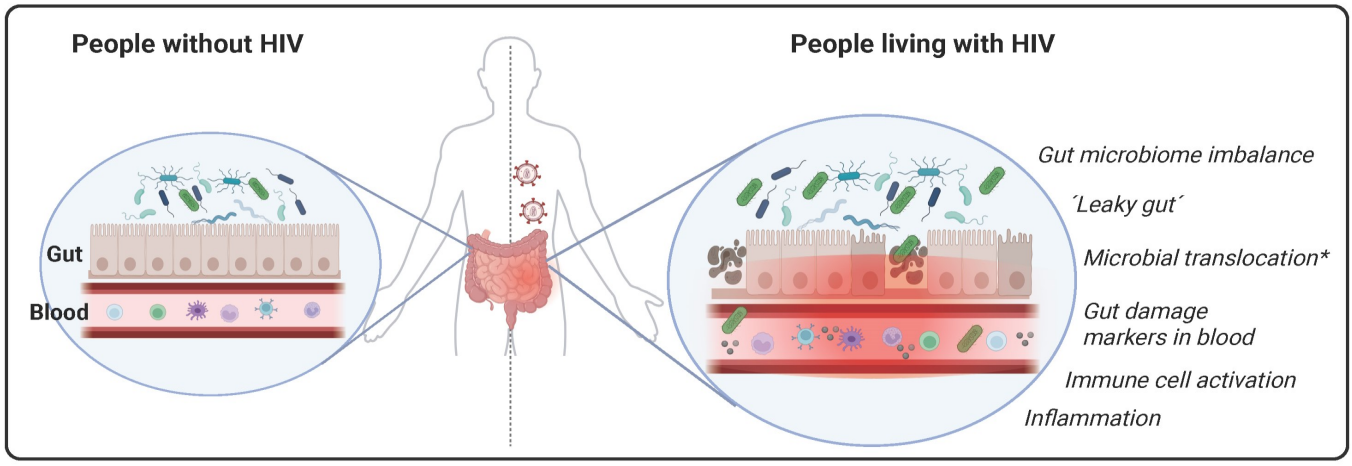

Figure 1: Imbalance of the gut microbiome of people with HIV has often reported with an enrichment of proteobacteria, even among persons on antiretrovirals. The loss of gut CD4 T cells and damage of gut epithelial cells, cause the so-called leaky gut. Under such conditions, microbial products reach the circulation where they drive immune cell activation and systemic inflammation.

* Microbial translocation doesn't necessarily imply the transfer of intact and living microbes, rather the transfer of microbial particles that are recognized by immune cells and sufficient to trigger immune cell activation

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Interventions that aim to modulate the gut microbiome in adults with HIV have explored probiotics supplements, fecal microbiome transplantation (FMT) and diet. In various disease settings, probiotics administration in humans have aimed to improve intestinal health through the colonization of the gut by the supplementation of beneficial bacteria, supporting the production of antimicrobials, the modulation of immune cells, and tropic effects driving the production of metabolites such as SCFAs. In PWH, randomized, double-blind placebo-controlled trials have administered *Lactobacillus*, *Bifidobacterium* or *Saccharomyces* species. However, none of these studies (reviewed in [37]) has shown an effect on gut permeability endpoints or on T cell activation. Randomized, double-blind placebo-controlled trials employing a cocktail of *Streptococcus thermophiles*, *Bifidobacteria* and *Lactobacilli* species or other open-label single arm studies did not either observe a convincing and consistent beneficial effects of probiotics intake on systemic measures of inflammation or microbial translocation [37-39]. In the PROMALTIA study, randomized administration of a mix containing prebiotics, *Saccharomyces boulardii*, omega-3/6 fatty acids, and amino acids in ART-treated adults with HIV showed no beneficial effect on T cell or microbiome measures [40]. These many studies underline the complexity of modulating the gut microbiome. Based on the premise that large quantitative input may matter, FMT was introduced as a mean to provide a substantial quantity of beneficial microbes. This approach was however challenged by a limited engraftment [41] or the lack of consistent changes on the metagenomic composition [42]. Despite these challenges, the ability of repeated FMT to improve the gut microbiome structure (i.e. increased diversity, higher abundance of *Lachnospiraceae*) and to reduce systemic levels of IFABP [43], suggest that FMT could remodel the gut microbiome and potentially help mitigate microbial translocation in PWH

Indirect approaches to modify the gut microbiome of PHW also evaluated lifestyle changes such as diet. Diet high in fat and sugar is generally known to change the composition of the gut microbiome and to favor inflammation [44]. A randomized controlled trial on Mediterranean diet with walnuts and extra virgin olive oil was found to be particularly effective among persons with high adherence; with the high adherence group showing improved lipid profiles and higher abundance of *Bifidobacterium* [45]. Interventional studies on the effect of Mediterranean diet in PWH are rare, but a substantial body of evidence in the general population [46] supports the idea that healthier dietary choices could remodel the gut microbiome and reduce inflammation in PWH. In fact, this may extend to lifestyle choices such as exercise routines. A recently published randomized control trial assigning cardiorespiratory, resistance and stretching training to self-reported sedentary PWH for 6 months reported reduced body mass index and an increase in gut microbial diversity [47]. These results are positive, but studies on the effect of exercise on the microbiome in the general population have generally been inconsistent with regards to diversity outcome measures and microbial composition [48]. Thus, it remains to be confirmed if and through which mechanisms a more active lifestyle would benefit the gut microbiome and microbial translocation in PWH.

Overall, numerous studies have employed different approaches in attempts to normalize the gut microbiome and limit microbial translocation in PWH. Across these various studies, variability in factors such as the precise nature of the intervention (e.g. Mediterranean diet is not always administered in the same manner), the duration of the intervention, the study outcomes measures, heterogeneity across study participants, are all factors that complicate comparison between studies. In addition, questions that are relevant to such research but have yet to be answered include: does the degree of inflammation at the start of study matter? Are combined strategies beneficial or even necessary? Which outcome measures could provide reliable insight into short or long-term effects? Future studies prioritizing well-powered, randomized clinical trials that combine microbiome interventions with lifestyle strategies, use standardized outcome measures will help understand how the gut microbiome and microbial translocation may be therapeutically targeted in PWH. Such an integrated approach could potentially help mitigate chronic inflammation and improve long-term health outcomes in people with HIV.

PRACTICAL CONSIDERATIONS

Diagnosis: At present, microbiome-related alterations are generally not part of routine clinical measures. Building on diagnostics measures that have been implemented in other diseases affecting the gut, a sensible recommendation is to measure blood levels of markers that are indicative of damage of gut epithelia and have consistently been associated with disease or immune impairment in PWH. Although sCD14 by itself does not inform on gut damage, combining blood measurements of both sCD14 and IFABP will indicate both gut damage and systemic immune activation. The precise threshold to pathological level is indicated by the certified diagnostic assay. For instance, the Institut für Medizinische Diagnostik (IMD) Berlin-Potsdam provides a threshold of 1827 pg/ml for IFABP.

Treatment: At the moment, solid evidence supporting clear therapeutics for people with HIV is still lacking. A practical recommendation may nonetheless include a healthy diet and lifestyle as the absence of this (e.g. high fat diet) has been shown to favor microbiome imbalance and a leaky gut.

References:

1. Human Microbiome Project, C., *Structure, function and diversity of the healthy human microbiome.* Nature, 2012. **486**(7402): p. 207-14.
2. Donaldson, G.P., S.M. Lee, and S.K. Mazmanian, *Gut biogeography of the bacterial microbiota.* Nat Rev Microbiol, 2016. **14**(1): p. 20-32.
3. Martin-Gallausiaux, C., et al., *SCFA: mechanisms and functional importance in the gut.* Proc Nutr Soc, 2021. **80**(1): p. 37-49.
4. Tincati, C., D.C. Douek, and G. Marchetti, *Gut barrier structure, mucosal immunity and intestinal microbiota in the pathogenesis and treatment of HIV infection.* AIDS Res Ther, 2016. **13**: p. 19.
5. Derikx, J.P., et al., *Non-invasive markers of gut wall integrity in health and disease.* World J Gastroenterol, 2010. **16**(42): p. 5272-9.
6. Landmann, R., et al., *Human monocyte CD14 is upregulated by lipopolysaccharide.* Infect Immun, 1996. **64**(5): p. 1762-9.
7. Ruderman, S.A., et al., *Biomarkers of microbial translocation and generalized inflammation are associated with frailty among people with HIV.* AIDS, 2025. **39**(2): p. 153-161.
8. Dillon, S.M., et al., *An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia.* Mucosal Immunol, 2014. **7**(4): p. 983-94.
9. Dinh, D.M., et al., *Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection.* J Infect Dis, 2015. **211**(1): p. 19-27.
10. Mutlu, E.A., et al., *A compositional look at the human gastrointestinal microbiome and immune activation parameters in HIV infected subjects.* PLoS Pathog, 2014. **10**(2): p. e1003829.
11. Noguera-Julian, M., et al., *Gut Microbiota Linked to Sexual Preference and HIV Infection.* EBioMedicine, 2016. **5**: p. 135-46.
12. Pinto-Cardoso, S., et al., *Fecal Bacterial Communities in treated HIV infected individuals on two antiretroviral regimens.* Sci Rep, 2017. **7**: p. 43741.

13.	Nganou-Makamdop, K. and D.C. Douek, *The Gut and the Translocated Microbiomes in HIV Infection: Current Concepts and Future Avenues.* Pathog Immun, 2024. **9**(1): p. 168-194.
14.	Badal, V.D., et al., *The Gut Microbiome, Aging, and Longevity: A Systematic Review.* Nutrients, 2020. **12**(12).
15.	Albenberg, L.G. and G.D. Wu, *Diet and the intestinal microbiome: associations, functions, and implications for health and disease.* Gastroenterology, 2014. **146**(6): p. 1564-72.
16.	Valeri, F. and K. Endres, *How biological sex of the host shapes its gut microbiota.* Front Neuroendocrinol, 2021. **61**: p. 100912.
17.	Gilbert, J.A., et al., *Current understanding of the human microbiome.* Nat Med, 2018. **24**(4): p. 392-400.
18.	Deschasaux, M., et al., *Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography.* Nat Med, 2018. **24**(10): p. 1526-1531.
19.	He, Y., et al., *Regional variation limits applications of healthy gut microbiome reference ranges and disease models.* Nat Med, 2018. **24**(10): p. 1532-1535.
20.	Kurilshikov, A., et al., *Large-scale association analyses identify host factors influencing human gut microbiome composition.* Nat Genet, 2021. **53**(2): p. 156-165.
21.	Touch, S., et al., *Human CD4+CD8alpha+ Tregs induced by Faecalibacterium prausnitzii protect against intestinal inflammation.* JCI Insight, 2022. **7**(12).
22.	Wang, H.B., et al., *Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein Claudin-1 transcription.* Dig Dis Sci, 2012. **57**(12): p. 3126-35.
23.	Dubourg, G., et al., *Gut microbiota associated with HIV infection is significantly enriched in bacteria tolerant to oxygen.* BMJ Open Gastroenterol, 2016. **3**(1): p. e000080.
24.	Serrano-Villar, S., et al., *The effects of prebiotics on microbial dysbiosis, butyrate production and immunity in HIV-infected subjects.* Raffatellu, M., et al., *Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut.* Nat Med, 2008. **14**(4): p. 421-8.MucosalImmunol, 2017. **10**(5): p. 1279-1293.
25.	Klase, Z., et al., *Dysbiotic bacteria translocate in progressive SIV infection.* Mucosal Immunol, 2015. **8**(5): p. 1009-20.
26.	Raffatellu, M., et al., *Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination om the gut.* Nat Med, 2008. **14**(4): p. 421-8.
27.	Litvak, Y., et al., *Dysbiotic Proteobacteria expansion: a microbial signature of epithelial dysfunction.* Curr Opin Microbiol, 2017. **39**: p. 1-6.
28.	Brix, S., et al., *Metagenomic heterogeneity explains dual immune effects of endotoxins.* J Allergy Clin Immunol, 2015. **135**(1): p. 277-80.
29.	Taib, N., et al., *Genome-wide analysis of the Firmicutes illuminates the diderm/monoderm transition.* Nat Ecol Evol, 2020. **4**(12): p. 1661-1672.
30.	Meng, Q., et al., *HIV-associated gut dysbiosis drives oncogenesis through metabolic-immune crosstalk: mechanisms and therapeutic implications.* Front Oncol, 2025. **15**: p. 1634388.
31.	Merlini, E., et al., *Evidence for polymicrobic flora translocating in peripheral blood of HIV-infected patients with poor immune response to antiretroviral therapy.* PLoS One, 2011. **6**(4): p. e18580.
32	Guo, X., et al., *Abnormal blood microbiota profiles are associated with inflammation and immune restoration in HIV/AIDS individuals.* mSystems, 2023. **8**(5): p. e0046723.
33.	Mac Cann, R., et al., *HIV, the gut microbiome and clinical outcomes, a systematic review.* PLoS One, 2024. **19**(12): p. e0308859.
34.	Vujkovic-Cvijin, I., et al., *HIV-associated gut dysbiosis is independent of sexual practice and correlates with noncommunicable diseases.* Nat Commun, 2020. **11**(1): p. 2448.
35.	Sperk, M., et al., *Fecal Metabolome Signature in the HIV-1 Elite Control Phenotype: Enrichment of Dipeptides Acts as an HIV-1 Antagist but a Prevotella Agonist.* J Virol, 2021. **95**(18): p. e0047921.
36.	Vesterbacka, J., et al., *Richer gut microbiota with distinct metabolic profile in HIV infected Elite Controllers.* Sci Rep, 2017. **7**(1): p. 6269.
37.	Reikvam, D.H., et al., *Probiotics to manage inflammation in HIV infection.* Curr Opin Infect Dis, 2020. **33**(1): p. 34-43.
38.	Presti, R.M., et al., *A Randomized, Placebo-Controlled Trial Assessing the Effect of VISBIOME ES Probiotic in People With HIV on An tiretroviral Therapy.* Open Forum Infect Dis, 2021. **8**(12): p. ofab550.
39.	Rousseau, R.K., et al., *Randomized, Blinded, Placebo-Controlled Trial of De Simone Formulation Probiotic During HIV-Associated Suboptimal CD4+ T Cell Recovery.* J Acquir Immune Defic Syndr, 2022. **89**(2): p. 199-207.

40.	Serrano-Villar, S., et al., *Effects of Immunonutrition in Advanced Human Immunodeficiency Virus Disease: A Randomized*
41.	Vujkovic-Cvijin, I., et al., *Limited engraftment of donor microbiome via one-time fecal microbial transplantation in treated HIV-infected individuals.* Gut Microbes, 2017. **8**(5): p. 440-450.
42.	Utay, N.S., et al., *Evaluation of Six Weekly Oral Fecal Microbiota Transplants in People with HIV.* Pathog Immun, 2020. **5**(1): p. 364-381.
43.	Serrano-Villar, S., et al., *Fecal microbiota transplantation in HIV: A pilot placebo-controlled study.* Nat Commun, 2021. **12**(1): p. 1139.
44.	Djuric, Z., *Dietary approaches for normalizing dysbiosis induced by high-fat, obesogenic diets.* Curr Opin Clin Nutr Metab Care, 2023. **26**(3): p. 293-301.
45.	Pastor-Ibanez, R., et al., *Adherence to a Supplemented Mediterranean Diet Drives Changes in the Gut Microbiota of HIV-1-Infected Individuals.*Nutrients, 2021. **13**(4).
46.	Khavandegar, A., et al., *Adherence to the Mediterranean diet can beneficially affect the gut microbiota composition: a systematic re view.*BMC Med Genomics, 2024. **17**(1): p. 91.
47.	Cooley, S.A., et al., *A randomized controlled trial to unveil the influence of an exercise intervention on brain integrity and gut microbiome* S*tructure in individuals with HIV.* AIDS, 2025.
48.	Min, L., et al., *Effects of Exercise on Gut Microbiota of Adults: A Systematic Review and Meta-Analysis.* Nutrients, 2024. **16**(7).

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