EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH
(EEJSAR) ISSN: 2992-4146
©EEJSAR Publications Volume 7 Issue 3 2025

Impact of Microbiome Modulation through Fecal Microbiota Transplantation (FMT) on HIV-Associated Inflammation and Immune Dysfunction

Bizimana Rukundo T.

Faculty of Biological Sciences Kampala International University Uganda

ABSTRACT

Chronic inflammation and immune dysfunction persist in people living with HIV (PLWH) despite effective antiretroviral therapy (ART), contributing to an increased risk of non-AIDS-defining comorbidities. Emerging evidence highlights the role of gut microbiome dysbiosis in driving these complications, characterized by reduced microbial diversity, microbial translocation, and systemic inflammation. Fecal microbiota transplantation (FMT), a therapeutic intervention that restores gut microbial balance, has shown promise in mitigating HIV-associated inflammation and immune dysfunction. This narrative review synthesized preclinical and clinical evidence on the impact of FMT in PLWH, exploring its mechanisms, efficacy, and challenges. Early-phase clinical trials in PLWH have reported improvements in gut microbial diversity, reductions in inflammatory markers, and modest immune recovery, though long-term efficacy and safety remain under investigation. Challenges include the heterogeneity of gut microbiome composition, the need for standardized FMT protocols, and potential risks such as infectious transmission and immune reactions. Future directions emphasize personalized FMT approaches, integration with probiotics and immune-based therapies, and advances in microbiome sequencing to optimize outcomes. This review employed a narrative methodology, drawing on a comprehensive analysis of preclinical and clinical studies to evaluate the potential of FMT as a therapeutic strategy for HIV-associated inflammation and immune dysfunction. By addressing these challenges, FMT and microbiome-based therapies offer hope for improving the health and quality of life of PLWH, bringing us closer to managing the residual effects of HIV infection.

Keywords: Fecal Microbiota Transplantation (FMT), HIV-associated inflammation, gut microbiome, immune dysfunction, microbial translocation.

INTRODUCTION

The human immunodeficiency virus (HIV) remains a significant global health burden, with approximately 38 million people living with the virus worldwide [1–3]. While antiretroviral therapy (ART) has dramatically improved the prognosis of HIV-infected individuals by suppressing viral replication and restoring immune function, it does not fully resolve chronic inflammation and immune dysfunction. These persistent abnormalities contribute to an increased risk of non-AIDS-defining comorbidities, such as cardiovascular disease, metabolic syndrome, and neurocognitive disorders, which are now the leading causes of morbidity and mortality in people living with HIV (PLWH) [4]. The underlying mechanisms driving these complications are multifactorial, but emerging evidence highlights the critical role of the gut microbiome in shaping systemic immune responses and inflammation.

The gut microbiome, a complex ecosystem of trillions of microorganisms, plays a pivotal role in maintaining immune homeostasis and barrier integrity [5, 6]. In HIV infection, the gut-associated lymphoid tissue (GALT) is an early site of viral replication and immune depletion, leading to microbial translocation, dysbiosis, and chronic inflammation. Dysbiosis, characterized by a loss of microbial diversity and an overrepresentation of pathogenic species, exacerbates immune activation and contributes to the persistence of HIV-associated inflammation [7]. Restoring gut microbiome balance has thus emerged as a promising therapeutic strategy to mitigate these effects.

Fecal microbiota transplantation (FMT), the transfer of fecal material from a healthy donor to a recipient, has gained recognition for its ability to restore microbial diversity and function in conditions such as recurrent *Clostridioides*

difficile infection. Its potential to modulate gut microbiome and reduce systemic inflammation has sparked interest in its application for HIV-associated immune dysfunction. This narrative review explores the impact of FMT on HIV-associated inflammation and immune dysfunction, synthesizing preclinical and clinical evidence, and discussing the challenges and future directions of this innovative approach.

The Gut Microbiome in HIV Pathogenesis

The gut microbiome is a dynamic and intricate community of bacteria, viruses, fungi, and archaea that coexists with the host in a mutually beneficial relationship [8]. In healthy individuals, the microbiome contributes to nutrient metabolism, pathogen resistance, and immune regulation. However, in HIV infection, the delicate balance of this ecosystem is disrupted. Early HIV infection is marked by the rapid depletion of CD4+ T cells in the GALT, leading to compromised mucosal integrity and increased permeability [9–11]. This "leaky gut" facilitates the translocation of microbial products, such as lipopolysaccharide (LPS), into systemic circulation, triggering chronic immune activation and inflammation.

Dysbiosis in PLWH is characterized by reduced microbial diversity, a decline in beneficial bacteria (e.g., *Bacteroides and Lactobacillus*), and an overgrowth of potentially pathogenic species (e.g., *Enterobacteriaceae and Proteobacteria*). These alterations are associated with elevated levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), and contribute to the persistence of immune dysfunction despite ART. The gut microbiome also influences the metabolism of antiretroviral drugs, potentially affecting their efficacy and toxicity. Thus, targeting the gut microbiome represents a novel therapeutic avenue to address the residual inflammation and immune dysfunction in PLWH.

Fecal Microbiota Transplantation: Mechanisms and Applications

FMT involves the transfer of processed fecal material from a healthy donor to a recipient, with the aim of restoring a balanced and functional gut microbiome [12]. The procedure has been most extensively studied and utilized for the treatment of recurrent *Clostridioides difficile* infection, where it has demonstrated remarkable efficacy. The success of FMT in this context has prompted investigations into its potential for other conditions characterized by dysbiosis, including inflammatory bowel disease, metabolic syndrome, and HIV-associated immune dysfunction.

The mechanisms by which FMT exerts its effects are multifaceted. By introducing a diverse and stable microbial community, FMT can outcompete pathogenic species, restore barrier integrity, and modulate immune responses. The transplanted microbiota produces metabolites, such as short-chain fatty acids (SCFAs), which have anti-inflammatory and immunomodulatory properties. SCFAs, including acetate, propionate, butyrate, enhance regulatory T cell (Treg) function, suppress pro-inflammatory cytokines, and promote epithelial repair. These effects collectively contribute to the resolution of inflammation and the restoration of immune homeostasis. In the context of HIV, FMT holds promise for addressing the dual challenges of dysbiosis and chronic inflammation. Preclinical studies in animal models have demonstrated that FMT can reduce microbial translocation, lower systemic inflammation, and improve immune reconstitution. These findings have laid the groundwork for clinical trials exploring the safety and efficacy of FMT in PLWH.

Preclinical Evidence: Insights from Animal Models

Animal models have provided valuable insights into the potential of FMT to modulate HIV-associated inflammation and immune dysfunction. Studies in simian immunodeficiency virus (SIV)-infected non-human primates, which closely mimic HIV infection in humans, have demonstrated that FMT can restore gut microbial diversity and reduce markers of microbial translocation and inflammation [13]. For example, FMT has been shown to decrease plasma levels of LPS and soluble CD14 (sCD14), a marker of monocyte activation, in SIV-infected macaques. These changes were associated with improved mucosal integrity and enhanced immune reconstitution. In addition to its effects on microbial translocation and inflammation, FMT has been shown to modulate the gut-immune axis in animal models [14]. The transplanted microbiota promotes the expansion of Tregs and the production of anti-inflammatory cytokines, such as IL-10, while suppressing pro-inflammatory responses. These immunomodulatory effects are mediated, in part, by the production of SCFAs, which serve as critical signaling molecules between the gut microbiota and the immune system. Despite these promising findings, challenges remain in translating preclinical results to human applications. Animal models do not fully recapitulate the complexity of human HIV infection, particularly the long-term effects of ART and the heterogeneity of gut microbiome composition. Nevertheless, these studies provide a strong rationale for investigating FMT in clinical trials.

Clinical Evidence: Early-Phase Trials and Safety Considerations

The clinical application of FMT in PLWH is still in its infancy, with a limited number of early-phase trials conducted to date. These studies have primarily focused on assessing the safety and feasibility of FMT, with secondary outcomes including changes in gut microbiome composition, microbial translocation, and systemic inflammation.

One of the pioneering clinical trials evaluated the safety and efficacy of FMT in ART-treated PLWH with incomplete immune reconstitution [15]. Participants received FMT from healthy donors, and the procedure was well-tolerated, with no serious adverse events reported. The study observed significant improvements in gut microbial diversity and reductions in markers of microbial translocation and inflammation. However, the effects on CD4+ T cell counts were modest, highlighting the need for further optimization of FMT protocols.

Another clinical trial explored the impact of FMT on metabolic parameters in PLWH with metabolic syndrome, a common comorbidity associated with chronic inflammation. The results indicated that FMT could improve insulin sensitivity and reduce systemic inflammation, as evidenced by decreases in CRP and IL-6 levels. These findings suggest that FMT may have broader applications in addressing HIV-associated comorbidities.

Safety remains a critical consideration in the clinical application of FMT. Potential risks include the transmission of infectious agents, the induction of immune reactions, and the long-term stability of the transplanted microbiota. Rigorous donor screening, standardized processing protocols, and close monitoring of recipients are essential to mitigate these risks. Additionally, the optimal timing, frequency, and route of FMT administration in PLWH require further investigation.

Challenges and Future Directions

While preclinical and early clinical evidence is promising, several challenges must be addressed to fully realize the potential of FMT in HIV-associated inflammation and immune dysfunction. One of the primary challenges is the heterogeneity of gut microbiome composition among PLWH, which may influence the response to FMT [16, 17]. Personalized approaches, tailored to the unique microbial and immunological profiles of individual patients, may enhance the efficacy of FMT.

Another challenge is the development of standardized protocols for FMT administration, including donor selection, fecal processing, and delivery methods. The use of encapsulated fecal microbiota or synthetic microbial consortia may offer more controlled and scalable alternatives to traditional FMT. Additionally, the integration of FMT with other therapeutic modalities, such as probiotics, prebiotics, and immune-based therapies, may enhance its effects.

Long-term safety and durability of FMT in PLWH also require further investigation. Longitudinal studies are needed to assess the stability of the transplanted microbiota, the persistence of its beneficial effects, and the potential for adverse outcomes. Advances in microbiome sequencing and metabolomics will provide deeper insights into the mechanisms underlying FMT and guide the development of next-generation microbiome-based therapies.

CONCLUSION

Fecal microbiota transplantation represents a promising therapeutic strategy for addressing HIV-associated inflammation and immune dysfunction. By restoring gut microbial diversity and function, FMT has the potential to reduce microbial translocation, lower systemic inflammation, and improve immune reconstitution. Preclinical studies in animal models have provided compelling evidence of their efficacy, and early-phase clinical trials have demonstrated its safety and feasibility in PLWH. However, significant challenges remain, including the heterogeneity of gut microbiome composition, the need for standardized protocols, and the long-term safety of FMT. Future research should focus on optimizing FMT protocols, developing personalized approaches, and integrating FMT with other therapeutic modalities. As our understanding of the gut-immune axis in HIV infection continues to evolve, FMT and other microbiome-based therapies hold great promises for improving the health and quality of life of PLWH. The convergence of scientific innovation and clinical research offers hope for a future where the residual effects of HIV infection can be effectively managed, bringing us closer to the goal of a functional cure.

REFERENCES

1. Ugo Alum, E., Okechukwu, U.P., Ifeanyi Obeagu, E., Maduabuchi Aja, P.: Reducing HIV Infection Rate in Women: A Catalyst to reducing HIV Infection pervasiveness in Africa. (2023). https://doi.org/10.58538/IJIAR/2048
2. Alum, E.U., Uti, D.E., Ugwu, O.P.C., Alum, B.N.: Toward a cure - Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine (United States). 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768
3. Mark, M.: The International Problem of HIV/AIDS in the Modern World: A Comprehensive Review of Political, Economic, and Social Impacts. https://doi.org/10.59298/ROJPHM/2024/414752
4. Falutz, J., Kirkland, S., Guaraldi, G.: Geriatric Syndromes in People Living with HIV Associated with Ageing and Increasing Comorbidities: Implications for Neurocognitive Complications of HIV Infection. Curr Top Behav Neurosci. 50, 301–327 (2019). https://doi.org/10.1007/7854_2019_119

5. Suchiita, A., Gupta, N., Nandi, K., Sonkar, S., Chandra, L.: Harmony Within: Unravelling the Microbiome–Immune System Symbiosis for Health. Advanced Gut & Microbiome Research. 2025, 9927379 (2025). https://doi.org/10.1155/AGM3/9927379
6. Shahid, A., Fatima, M., Saleem, M., Khan, I., Ali, U., Fareed, Z., Qureshi, M.A.: From Microbes to Immunity: A Comprehensive Review of Microbiome Modulation. Journal of Health and Rehabilitation Research. 3, 801–807 (2023). https://doi.org/10.61919/JHRR.V3I2.238
7. Fakharian, F., Thirugnanam, S., Welsh, D.A., Kim, W.K., Rappaport, J., Bittinger, K., Rout, N.: The Role of Gut Dysbiosis in the Loss of Intestinal Immune Cell Functions and Viral Pathogenesis. Microorganisms 2023, Vol. 11, Page 1849. 11, 1849 (2023). https://doi.org/10.3390/MICROORGANISMS11071849
8. Shang, Z., Pai, L., Patil, S.: Unveiling the dynamics of gut microbial interactions: a review of dietary impact and precision nutrition in gastrointestinal health. Front Nutr. 11, 1395664 (2024). https://doi.org/10.3389/FNUT.2024.1395664/BIBTEX
9. Alum, E.U., Obeagu, E.I., Ugwu, O.P.C., Samson, A.O., Adepoju, A.O., Amusa, M.O.: Inclusion of nutritional counseling and mental health services in HIV/AIDS management: A paradigm shift. Medicine. 102, e35673 (2023). https://doi.org/10.1097/MD.0000000000035673
10. Alum, E.U., Uti, D.E., Ugwu, O.P.-C., Alum, B.N.: Toward a cure – Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine. 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768
11. Moretti, S., Schietroma, I., Sberna, G., Maggiorella, M.T., Sernicola, L., Farcomeni, S., Giovanetti, M., Ciccozzi, M., Borsetti, A.: HIV-1–Host Interaction in Gut-Associated Lymphoid Tissue (GALT): Effects on Local Environment and Comorbidities. International Journal of Molecular Sciences 2023, Vol. 24, Page 12193. 24, 12193 (2023). https://doi.org/10.3390/IJMS241512193
12. Nicco, C., Paule, A., Konturek, P., Edeas, M.: From Donor to Patient: Collection, Preparation and Cryopreservation of Fecal Samples for Fecal Microbiota Transplantation. Diseases 2020, Vol. 8, Page 9. 8, 9 (2020). https://doi.org/10.3390/DISEASES8020009
13. Ouyang, J., Yan, J., Zhou, X., Isnard, S., Harypursat, V., Cui, H., Routy, J.P., Chen, Y.: Relevance of biomarkers indicating gut damage and microbial translocation in people living with HIV. Front Immunol. 14, 1173956 (2023). https://doi.org/10.3389/FIMMU.2023.1173956/PDF
14. Adamkova, P., Hradicka, P., Gancarcikova, S., Kassayova, M., Ambro, L., Bertkova, I., Maronek, M., Iannaccone, S.F., Demeckova, V.: Single Donor FMT Reverses Microbial/Immune Dysbiosis and Induces Clinical Remission in a Rat Model of Acute Colitis. Pathogens 2021, Vol. 10, Page 152. 10, 152 (2021). https://doi.org/10.3390/PATHOGENS10020152
15. Johnson, S.D., Pino, M., Acharya, A., Clain, J.A., Bose, D., Nguyen, K., Harper, J., Villinger, F., Paiardini, M., Byrareddy, S.N.: Interleukin-21 and anti-α4β7 dual therapy during ART promotes immunological and microbiome responses in SIV-infected macaques. JCI Insight. (2025). https://doi.org/10.1172/JCI.INSIGHT.184491
16. Blanco, J.R., Negredo, E., Bernal, E., Blanco, J.: Impact of HIV infection on aging and immune status. Expert Rev Anti Infect Ther. 19, 719–731 (2021). https://doi.org/10.1080/14787210.2021.1848546
17. Ouyang, J., Yan, J., Zhou, X., Isnard, S., Harypursat, V., Cui, H., Routy, J.P., Chen, Y.: Relevance of biomarkers indicating gut damage and microbial translocation in people living with HIV. Front Immunol. 14, 1173956 (2023). https://doi.org/10.3389/FIMMU.2023.1173956/PDF

CITE AS: Bizimana Rukundo T. (2025). Impact of Microbiome Modulation through Fecal Microbiota Transplantation (FMT) on HIV-Associated Inflammation and Immune Dysfunction. EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH. 7(3):128-131