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Impact of Nutritional Supplementation on Immune Recovery in Malnourished Adults Initiating ART: A Multicenter Controlled Trial

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ABSTRACT

Malnutrition poses a significant challenge to immune recovery among adults initiating antiretroviral therapy (ART), particularly in resource-limited settings where HIV and food insecurity co-occur. This review assesses the effect of nutritional supplementation on immunological outcomes in malnourished adults starting antiretroviral therapy (ART), with a focus on evidence from multicenter, controlled trials. Malnutrition, characterized by macro- and micronutrient deficiencies, impairs immune cell regeneration, exacerbates systemic inflammation, and compromises ART efficacy through poor absorption and heightened susceptibility to opportunistic infections. Nutritional supplementation, especially when combining macronutrients with immunomodulatory micronutrients like zinc, selenium, and vitamins A, D, and E, has shown potential to accelerate CD4+ T-cell recovery, reduce early mortality, and improve functional health outcomes. Clinical trials reviewed reveal modest but clinically meaningful improvements; however, heterogeneity in supplementation strategies, adherence, and baseline nutritional status limits the generalizability of these findings. This article was developed using a narrative review methodology that synthesizes findings from peer-reviewed multicenter controlled trials across sub-Saharan Africa and Southeast Asia. Context-specific implementation, integration with HIV care frameworks, and consideration of local dietary practices are critical to optimizing the benefits of supplementation. Future research should prioritize biomarker-guided approaches, long-term follow-up, and the role of the gut microbiome to refine nutrition-based interventions. Nutritional support remains a vital, evidence-based component of comprehensive HIV treatment strategies.

Keywords: Nutritional supplementation, Immune recovery, Antiretroviral therapy (ART), Malnutrition, HIV/AIDS

INTRODUCTION

Malnutrition and HIV/AIDS form a deleterious synergy, particularly in resource-limited settings where food insecurity and high HIV prevalence co-occur [1–3]. Malnourished individuals living with HIV (PLHIV) present with significantly weakened immune systems, impaired gastrointestinal absorption, and elevated susceptibility to opportunistic infections. The initiation of antiretroviral therapy (ART) is a critical juncture in HIV care [4, 5]. However, malnutrition at the point of ART commencement has been consistently associated with delayed immune reconstitution, increased early mortality, and suboptimal treatment adherence. Consequently, addressing nutritional deficits alongside ART initiation has emerged as an important adjunctive strategy to bolster immune recovery and improve overall treatment outcomes. The immune system requires a broad spectrum of macro- and micronutrients to function optimally. Key nutrients such as proteins, vitamins A, C, D, E, B-complex, and trace elements like zinc and selenium have immunomodulatory roles that influence T-cell proliferation, cytokine signaling, and oxidative stress modulation [6, 7]. In malnourished adults initiating ART, deficits in these nutrients may impair immune cell regeneration, blunt CD4+ T-cell recovery, and exacerbate systemic inflammation. While ART suppresses viral replication and gradually restores immune function, nutritional supplementation may accelerate and enhance this process by correcting deficiencies that compromise cellular immunity. Multicenter controlled trials assessing the impact of nutritional interventions on immune recovery in malnourished adults initiating ART have produced valuable but varied results. Some studies indicate improved CD4+ T-cell counts, weight gain, and reduced morbidity, while others demonstrate marginal benefits, highlighting the need for contextualized and evidence-based

supplementation protocols [8]. This review synthesizes findings from multicenter controlled trials to evaluate the efficacy of nutritional supplementation in enhancing immune recovery in malnourished adults at ART initiation. The article explores underlying immunological mechanisms, reviews clinical outcomes across diverse geographic settings, and identifies critical considerations for the integration of nutrition-based interventions in comprehensive HIV care.

Malnutrition and Immune Dysfunction in HIV

Malnutrition and HIV/AIDS interact in a vicious cycle that compounds immune suppression [9, 10]. Malnutrition, whether due to macronutrient deficiencies or micronutrient insufficiency, impairs both innate and adaptive immunity. In HIV-infected individuals, this translates into reduced lymphocyte counts, impaired mucosal defenses, increased gut permeability, and systemic inflammation. As a result, malnourished PLHIV are more likely to present with advanced disease at ART initiation and to experience delayed immune restoration.

Nutritional status, particularly body mass index (BMI) and serum albumin levels, has been identified as a strong predictor of early mortality in adults commencing ART [11]. Studies show that individuals with BMI below 18.5 kg/m^2 are more likely to experience opportunistic infections, slow CD4+ recovery, and adverse treatment outcomes. The immunological deficits observed in malnourished adults are not merely a consequence of HIV-related waste but are rooted in biochemical inadequacies that hinder immune cell differentiation, signal transduction, and antigen response. Furthermore, intestinal malabsorption, a common feature in malnourished HIV-positive individuals, reduces the bioavailability of orally administered ART and nutrients. This leads to poor drug absorption, low serum nutrient concentrations, and higher systemic inflammation. The combination of poor nutritional intake, increased nutrient loss, and inefficient absorption severely limits the potential for immune recovery unless addressed concurrently with ART.

Mechanisms of Nutritional Supplementation in Immune Recovery

Nutritional supplementation offers immunological benefits through multiple pathways. Protein-energy supplements enhance T-cell regeneration by providing substrates essential for cell proliferation and tissue repair [12]. Micronutrients play pivotal roles in immune signaling, redox balance, and leukocyte function. For instance:

i. **Zinc** supports thymic function, T-cell development, and anti-inflammatory cytokine production [13].
ii. **Vitamin A** modulates mucosal immunity and enhances epithelial integrity.
iii. **Vitamin D** regulates T-helper cell differentiation and suppresses excessive inflammation [14].
iv. **Selenium** acts as an antioxidant and supports cytotoxic lymphocyte activity.

Supplementation also mitigates the oxidative stress commonly observed in ART initiation, where immune reconstitution may lead to transient immune activation and elevated reactive oxygen species. By restoring antioxidant capacity, nutrients such as vitamin E and selenium may reduce inflammation-driven tissue damage and support a more favorable immune milieu.

Clinical trials have also demonstrated that nutrient repletion improves gut barrier function, thereby reducing microbial translocation and systemic immune activation key factors that impair CD4+ recovery. Given these mechanisms, supplementation is theorized to provide a synergistic boost to ART-induced viral suppression and immunological restoration.

Evidence from Multicenter Controlled Trials

Several multicenter controlled trials have investigated the role of nutritional supplementation in improving immune recovery among malnourished adults initiating ART, particularly in sub-Saharan Africa and Southeast Asia where food insecurity is prevalent [15].

One landmark trial conducted across Malawi, Zambia, and Tanzania evaluated the effects of lipid-based nutrient supplements (LNS) containing vitamins, minerals, and macronutrients in malnourished adults starting ART [16]. The study found a modest increase in CD4+ counts and greater weight gain in the intervention group compared to controls receiving standard care. Participants who received supplementation within the first 12 weeks of ART also exhibited reduced rates of early mortality. Another randomized trial in Uganda assessed high-protein supplementation with added micronutrients versus standard energy-dense foods. The results indicated improved lean body mass and moderate increases in CD4+ T-cell counts, suggesting that both quantity and quality of protein intake are important for immune reconstitution. In Ethiopia, a trial testing the efficacy of multiple micronutrient powders (MNPs) in ART-naïve adults found significant improvements in serum zinc and vitamin D levels but no statistically significant change in CD4+ counts [17]. However, the supplemented group showed fewer ART interruptions and reduced gastrointestinal symptoms, indicating potential ancillary benefits. Overall, trial results have been heterogeneous, influenced by supplementation type, duration, adherence, and baseline nutritional status. Nonetheless, the consensus points toward modest but clinically meaningful improvements in immune recovery, especially in severely malnourished individuals or those with concurrent gastrointestinal disorders.

Variability in Supplementation Strategies and Outcomes

Differences in supplementation strategies ranging from macronutrient-rich ready-to-use therapeutic foods (RUTFs) to micronutrient powders and fortified porridges yield varying impacts on immune outcomes. The timing,

composition, and dosage of supplements are critical factors influencing efficacy. Macronutrient supplements, particularly those rich in proteins and essential fatty acids, support overall metabolic function and promote weight gain, which is often a surrogate marker for improved immune recovery [18]. However, without accompanying micronutrients, macronutrient supplementation alone may fail to correct critical immunological deficits. Conversely, micronutrient-only approaches may restore biochemical deficiencies but have limited impact on weight restoration or systemic metabolism. A combined approach employing balanced macro- and micronutrient supplementation is increasingly advocated to maximize benefits.Adherence is another critical determinant of success. Trials have noted that palatability, gastrointestinal side effects, and logistical barriers such as transport and food insecurity may affect adherence rates [19]. In addition, co-administration with ART must be carefully managed to avoid drug-nutrient interactions and to ensure optimal timing for absorption. Geographical variability, including regional differences in baseline nutritional deficiencies, dietary patterns, and infection burdens (e.g., co-endemic tuberculosis or parasitic infections), further complicates standardization of supplementation protocols. Thus, context-specific interventions that are culturally acceptable and nutritionally tailored are essential for improving immune outcomes

Policy and Programmatic Implications

The integration of nutritional supplementation into routine HIV care has significant policy implications [20]. While ART scale-up remains a central priority in global HIV responses, addressing underlying malnutrition is increasingly recognized as vital for improving long-term outcomes. Programmatic incorporation of nutrition into ART initiation protocols may enhance immune recovery, improve functional status, and reduce healthcare utilization. Several national HIV programs have adopted nutrition assessment, counseling, and support (NACS) frameworks, which include screening for malnutrition, provision of therapeutic or supplementary foods, and follow-up during ART. These interventions are especially critical during the first 3–6 months of ART, when the risk of mortality is highest among malnourished individuals. From a cost-effective standpoint, early nutritional intervention may reduce hospital admissions, accelerate functional recovery, and improve ART adherence offsetting the additional costs of supplementation. However, sustained implementation requires investment in supply chains, community health worker training, and monitoring systems. Future interventions must also consider the scalability of supplementation programs, the sustainability of local food-based solutions, and the potential of leveraging existing community networks to support adherence. Additionally, greater emphasis on pre-ART nutritional screening and early detection of malnutrition can help optimize the timing and targeting of supplementation.

Research Gaps and Future Directions

Despite accumulating evidence, important knowledge gaps persist. Many trials have limited follow-up durations and small sample sizes, making it difficult to evaluate long-term immunological and virological outcomes. Moreover, few studies have stratified results based on sex, age, or comorbidities, factors which may influence nutritional needs and immune responses. Biomarker-based assessments such as levels of interleukin-6 (IL-6), C-reactive protein (CRP), and soluble CD14 could offer deeper insight into the immunological effects of supplementation [21]. Furthermore, understanding the gut microbiome's role in mediating nutrition-immunity interactions may open avenues for novel interventions, including prebiotic and probiotic formulations. There is also a need for multicenter trials comparing different supplementation types, dosages, and administration schedules. Adaptive trial designs could help identify optimal regimens based on real-time immunological feedback. Integrative approaches combining nutritional support with psychosocial and economic interventions may further enhance ART outcomes, especially in socioeconomically marginalized populations. In the long term, building nutrition-sensitive HIV care models supported by national policies and aligned with broader food security strategies will be essential in achieving comprehensive, equitable care for malnourished PLHIV.

CONCLUSION

Malnutrition remains a formidable barrier to effective HIV care, particularly at ART initiation, where immune restoration is critical for clinical recovery. The evidence reviewed in this article underscores the role of nutritional supplementation in enhancing immune outcomes among malnourished adults beginning ART. While ART alone suppresses viral replication, it does not address the underlying nutrient deficits that compromise immune function, particularly in resource-limited settings. Multicenter controlled trials reveal that supplementation, particularly with combined macro- and micronutrients offers modest but clinically significant benefits in terms of CD4+ recovery, weight gain, and reduced morbidity. However, variability in outcomes reflects differences in supplementation protocols, adherence, and baseline nutritional status, necessitating context-specific strategies. Effective implementation of nutritional interventions must consider not only biological efficacy but also cultural acceptability, logistical feasibility, and integration into existing HIV care frameworks. Future research should aim to refine supplementation strategies using biomarker-guided approaches and explore synergistic interventions targeting microbiome, gut health, and systemic inflammation. Ultimately, embedding nutrition into ART programs is not merely an adjunct but a fundamental component of holistic HIV care. Addressing malnutrition through evidence-based supplementation offers a tangible path to improving immune recovery, enhancing treatment success, and ensuring better long-term health outcomes for malnourished PLHIV

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