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MICRONUTRIENT DEFICIENCIES IN HIV: IMPACT ON DISEASE PROGRESSION AND RESPONSE TO ANTIRETROVIRAL THERAPY

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ABSTRACT

HIV infection remains a chronic condition of high clinical relevance, even in the face of advances provided by antiretroviral therapy. In this context, micronutrient deficiencies have been associated with poorer immune response, disease progression, increased risk of clinical complications, and incomplete recovery of CD4+ T lymphocytes. The present study aimed to analyze the available scientific evidence on the impact of micronutrient deficiencies on HIV progression and response to antiretroviral therapy. This is an integrative literature review, with a systematic approach, conducted from studies indexed in recognized scientific databases, including systematic reviews, meta-analyses, randomized clinical trials, cohorts, and observational studies. Twenty studies were selected that addressed micronutrients such as vitamin A, vitamin B12, vitamin D, zinc, selenium, and multivitamins in people living with HIV.Findings indicated that deficiencies in vitamin A and vitamin B12 were associated with clinical progression and mortality, while low vitamin D levels were related to virologic failure and lower CD4 recovery during antiretroviral therapy. Zinc showed an association with immunologic failure and gastrointestinal morbidity, and selenium demonstrated potential association with viral load, survival, and immune response. Although supplementation may provide benefits in specific contexts, especially in individuals with confirmed deficiency or nutritional vulnerability, the results remain heterogeneous and depend on the micronutrient assessed, the study population, baseline nutritional status, and the use of antiretroviral therapy. It is concluded that micronutrient deficiencies may act as markers of severity and possible cofactors in HIV progression, and individualized nutritional assessment is recommended as a complementary strategy to clinical care.

Keywords:hiv; micronutrients; antiretroviral therapy; nutritional status.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a chronic condition of high clinical and epidemiological relevance, even after the significant advances provided by antiretroviral therapy (ART). Expanded access to treatment has profoundly changed the natural course of the disease, reduced mortality, improved survival, and transformed HIV into a manageable condition in the long term. However, the clinical and immunological recovery of people living with HIV does not depend exclusively on viral suppression. Nutritional, inflammatory, metabolic and immunological factors continue to influence disease progression, the therapeutic response, and the quality of life of these individuals [1,3,10,18-20].

Among these factors, micronutrient deficiencies have received increasing attention in the scientific literature due to their relationship with immunosuppression, oxidative stress, persistent inflammation, hematological changes, higher risk of opportunistic infections, and poorer immunological recovery. Vitamins and minerals play essential roles in maintaining the integrity of epithelial barriers, in the differentiation and activation of immunological cells, in the antioxidant response, in the production of cytokines, and in the regulation of metabolic processes related to the host's defense. Thus, micronutrient deficiency may represent not only a consequence of chronic HIV infection, but also a possible cofactor associated with clinical progression and an incomplete response to ART [3-6].

The pathophysiology of nutritional deficiencies in HIV is multifactorial. People living with HIV may have inadequate food intake, greater metabolic demand, poor intestinal absorption, alterations in the microbiota, chronic inflammation, infections opportunistic infections, weight loss, recurrent diarrhea, and treatment-related adverse effects. These mechanisms contribute to the reduction of the serum and tissue levels of vitamins and minerals, even in individuals using ART. In addition, the persistence of immune activation and oxidative stress may increase the consumption of micronutrients antioxidants and further compromise nutritional balance [4,5,10].

The literature indicates that some specific deficiencies appear to have

greater clinical relevance in the context of HIV. Vitamin A has been associated with mucosal integrity, cellular immunity, and mortality, especially in classic studies conducted in vulnerable populations. A deficiency of vitamin B12 has been linked to faster disease progression, suggesting a possible impact on hematological, neurological, and immunological parameters. Zinc plays an essential role in lymphocyte function, maintenance of the intestinal barrier, and the response against infections, while selenium is involved in antioxidant mechanisms and may interfere with viral progression and immune function. Vitamin D, in turn, gained prominence in the era of ART due to its association with recovery of CD4+ T lymphocytes, clinical progression, and virologic failure in different population contexts [6-13, 18-20].

Although ART is the main determinant of viral suppression and the reduction of morbidity and mortality associated with HIV, evidence indicates that micronutrient deficiencies may persist even in treated patients. This condition is particularly relevant in individuals with incomplete immune recovery, low CD4 count, history of opportunistic infections, anemia, and chronic diarrhea, food insecurity or persistent inflammatory conditions. Studies with patients using HAART/ART have shown that changes in zinc, vitamin D, selenium, and other micronutrient levels may be associated with unfavorable clinical and laboratory outcomes, including poorer immune recovery and a higher risk of virologic failure [3, 10, 18-20].

Micronutrient supplementation in HIV, however, should be interpreted with caution. Systematic reviews and meta-analyses indicate that the effects of supplementation vary depending on the type of micronutrient, the dose used, baseline nutritional status, disease stage, the presence or absence of ART, age, pregnancy status, and the outcomes analyzed. In some studies, interventions with multivitamins, zinc, or selenium showed benefits on immunological parameters, viral load, diarrhea, anemia, or clinical progression. However, results are not uniform, and indiscriminate supplementation should not be understood as a substitute for ART or as a universal intervention for all people living with HIV [1-3, 12-16].

In this regard, it is necessary to critically analyze the evidence

available on the relationship between micronutrient deficiencies and clinical evolution of HIV, especially in the contemporary context of ART. Understanding this topic can help develop more integrated care strategies that link antiretroviral treatment, nutritional assessment, laboratory monitoring, and individualized intervention. This approach is particularly important in populations with greater social, food, and clinical vulnerability, in which nutritional deficiencies may worsen immunosuppression, compromise adherence to therapy, and negatively influence health outcomes.

Given this, this integrative review aims to analyze the scientific evidence available on micronutrient deficiencies in people living with HIV, with emphasis on the impact of these changes on disease progression, immune response, recovery of CD4+ T lymphocytes, viral load, mortality, and the response to antiretroviral therapy. It also seeks to discuss the potential role of micronutrient supplementation as a strategy complementary and individualized in the care of people living with HIV, considering its benefits, limitations, and clinical implications in light of the current scientific literature [1-3, 18-20].

METHODOLOGY

This is an integrative literature review, with a systematic approach, developed with the aim of gathering, analyzing, and synthesizing scientific evidence on micronutrient deficiencies in people living with HIV and their impacts on disease progression, immune response, and response to antiretroviral therapy. The choice of an integrative review is justified because it allows the inclusion of different methodological designs, such as systematic reviews, meta-analyses, randomized clinical trials, cohort studies, observational studies, and clinical reviews, enabling a broad and critical understanding of the phenomenon under investigation.

The guiding question was structured from the following formulation: what scientific evidence is available on the relationship between micronutrient deficiencies and disease progression, immune recovery, viral load,

Mortality and response to antiretroviral therapy in people living with HIV? From this question, the following components were defined as central elements of the search: a population composed of people living with HIV; exposure related to micronutrient deficiency or supplementation; and outcomes associated with clinical progression, CD4+ T lymphocyte count, viral load, virologic failure, mortality, anemia, diarrhea, immunologic failure, and response to ART.

The bibliographic search was conducted in internationally recognized scientific databases, with priority for PubMed/MEDLINE, Cochrane Library, Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), ScienceDirect, SpringerLink, and Google Scholar, used as a complement for tracking relevant studies and cross-checking references. Controlled descriptors and free-text terms in English and Portuguese were considered, combined using Boolean operators. Among the main terms used were: “HIV”, “Human Immunodeficiency Virus”, “AIDS”, “micronutrients”, “micronutrient deficiency”, “vitamin deficiency”, “vitamin A”, “vitamin B12”, “vitamin D”, “zinc”, “selenium”, “antiretroviral therapy”, “HAART”, “CD4 count”, “viral load”, “disease progression”, “immune recovery”, “virological failure”,“mortality”, “anemia” and “diarrhea”. In Portuguese, corresponding terms were used, such as “HIV”,“micronutrient deficiencies”,“vitamin A” “vitamin B12” “vitamin , , D”, “zinc”, “selenium”, “antiretroviral therapy”, “disease progression”,“viral load” and “CD4+ T lymphocytes”.

Studies published in indexed scientific journals were included, with availability of methodological data and results compatible with the review objective. Systematic reviews, meta-analyses, randomized clinical trials, prospective studies, observational studies, cohorts, and clinical reviews of scientific relevance were considered eligible, provided they addressed the relationship between micronutrients and clinical, immunological, virological, or therapeutic outcomes in people living with HIV. Classic studies prior to the consolidation of modern antiretroviral therapy were also included when they had historical and scientific relevance for understanding the association between nutritional deficiencies and disease progression. This methodological decision was adopted because an important part of the

Evidence on vitamin A, vitamin B12, selenium, and the clinical progression of HIV was produced in periods prior to the widespread availability of antiretroviral therapy, maintaining interpretive value for the analysis of the physiopathological and prognostic aspects of the topic.

Articles that did not have a direct relationship with HIV and micronutrients were excluded; studies focused exclusively on macronutrients without evaluating vitamins or minerals; duplicate publications; abstracts without full text available; letters to the editor; opinions without a defined methodological basis; studies with insufficient data to extract the outcomes of interest; and publications without adequate traceability in recognized scientific databases. Work addressing nutritional supplementation in a generic manner was also excluded, without discrimination of the micronutrients assessed or without association with clinical, immunological, virological, or therapeutic indicators.

The study selection process took place in successive stages. Initially, publications were identified through the combination of the descriptors in the selected databases. Next, the titles and abstracts were reviewed, excluding the studies clearly incompatible with the topic. The potentially eligible articles were assessed through full-text reading, considering alignment with the review objective, methodological quality, relevance of outcomes, and contribution to understanding the relationship between micronutrients, HIV progression, and response to ART. After this screening, 20 studies were selected to compose the final review base, encompassing evidence from different levels and population contexts.

Data extraction was performed using a previously structured analytical matrix, including the following variables: author and year of publication, country or study context, methodological design, population studied, micronutrient assessed, relationship with antiretroviral therapy, main findings, methodological limitations, and the contribution of the article. The prioritized outcomes were clinical disease progression, mortality, CD4+ T-lymphocyte count, viral load, virologic failure, immunologic failure, immunologic recovery after initiation of ART, anemia, diarrhea, and indicators of nutritional impairment. This strategy made it possible to organize the evidence into thematic categories and identify areas of convergence, divergence, and scientific gaps.

The data analysis was conducted descriptively and critically, with a narrative synthesis of the findings. The studies were grouped by thematic axes, considering the type of micronutrient assessed and the main outcomes associated with it. Thus, the discussion of the results was organized around five main dimensions: micronutrient deficiencies as markers of HIV progression; the role of selenium, zinc, and vitamins in modulating immunity; the association between vitamin D, virological failure, and CD4 recovery during ART; effects of micronutrient supplementation as an adjuvant strategy; and limitations of the evidence available in the contemporary antiretroviral therapy setting.

Because this is an integrative review based on previously published studies available in scientific databases, there was no direct involvement of human beings, collection of primary data, or need to submit to an Ethics Committee for Research. The principles of scientific integrity, traceability of sources, fidelity to the original findings, and judicious use of citations were respected. The references were organized in Vancouver style, according to the editorial guidelines of the Ipedss Scientific Journal, maintaining numbering in accordance with the order of use during the development of the article.

RESULTS

This integrative review included 20 studies that addressed the relationship between micronutrient deficiencies, HIV infection progression, and response to antiretroviral therapy. The analyzed base consisted of systematic reviews, meta-analyses, trials clinical randomized, cohort studies, observational studies, and clinical reviews, enabling a broad assessment of the effects of vitamins and minerals on immunological, virological, clinical and nutritional in people living with HIV.

In general, the studies showed that micronutrient deficiencies may be associated with worse clinical outcomes, especially when they involve vitamin A, vitamin B12, vitamin D, zinc, and selenium. These micronutrients were related to disease progression, reduced CD4+ T-lymphocyte counts, increased mortality, and a higher risk of failure

viral, lower immune recovery, anemia, diarrhea, and greater vulnerability to opportunistic infections [3-13, 18-20]. However, the results also showed that the benefits of supplementation are not uniform and depend on the clinical context, baseline nutritional status, the stage of the disease, the presence or absence of ART, and the characteristics of the studied population [1-3].

The analysis of the studies made it possible to organize the findings into five main axes: deficiencies of micronutrients as markers of HIV progression; selenium, viral load, and mortality; zinc, immune failure, and gastrointestinal morbidity; vitamin D, CD4 recovery, and virological failure; and multivitamin supplementation as an adjuvant strategy in specific contexts.

Micronutrient Deficiencies as markers of HIV progression

Classic observational studies showed an association between micronutrient deficiency and an unfavorable progression of HIV infection. Baum et al. identified that changes in micronutrient levels—especially vitamin A and vitamin B 12—were related to disease progression in individuals infected with HIV-1 [6]. In line with this, Tang et al. observed that low serum concentrations of vitamin B12 were associated with faster progression of infection, suggesting that this micronutrient may act as a marker of clinical and immunological risk [7].

Vitamin A also stood out in early studies on nutrition and HIV. Semba et al. reported increased mortality associated with vitamin A deficiency in individuals infected with HIV-1, while another study from the same group found that deficiency of this vitamin, when associated with wasting, predicted a higher risk of death in people who inject drugs living with HIV [8,9]. These findings indicate that hypovitaminosis A may reflect both poorer nutritional status and greater clinical severity of infection.

In addition, clinical and mechanistic reviews pointed out that deficiencies of vitamins and minerals may interfere with essential immune mechanisms, including lymphocyte function, the antioxidant response, mucosal integrity, inflammatory regulation, and resistance to opportunistic infections [4,5]. Thus, the results suggest that deficiencies micronutritional should not be

interpreted only as secondary manifestations of the disease, but as components associated with immune status and clinical prognosis.

Selenium, Viral Load, Immunity, and Mortality

Selenium was one of the micronutrients most frequently associated with disease progression and mortality. In a prospective cohort study conducted with pregnant women living with HIV-1 in Tanzania, Kupka et al. observed that reduced levels of selenium were associated with accelerated disease progression and worse survival outcomes [11]. This finding suggests that selenium may play a relevant role in antioxidant defense and in maintaining immune function in vulnerable populations.

In the area of interventions, Hurwitz et al. showed, in a randomized clinical trial, that selenium supplementation was associated with suppression of HIV-1 viral load progression and with favorable indirect effects on the count of CD4+ T lymphocytes [12]. Although the study does not allow selenium to be considered a substitute for ART, its findings indicate a possible adjuvant role in specific contexts, especially when there is deficiency or nutritional risk.

On the other hand, the trial conducted by Kupka et al. in pregnant women infected with HIV evaluated selenium supplementation on maternal and infant outcomes, showing that effects may vary according to the population, methodological design, and outcome analyzed [15]. Thus, the findings on selenium point to biological and clinical relevance, but also reinforce the need for individualized assessment before any supplementation proposal.

Zinc, Immunological Failure, and Gastrointestinal Morbidity

Zinc showed a strong relationship with immunity, intestinal integrity, and gastrointestinal morbidity. Jones et al. demonstrated that changes in micronutrient levels, including zinc, could persist in patients using HAART, indicating that antiretroviral therapy does not eliminate completely the risk of nutritional deficiency [10]. This finding is relevant because it shows that viral suppression and clinical improvement do not necessarily correspond to normalization of the micronutritional status.

In a randomized clinical trial, Baum et al. assessed the supplementation of zinc in adults living with HIV and

they observed a reduction in immunological failure and in episodes of diarrhea [13]. These findings suggest that zinc may play an important role in maintaining immune function and the intestinal barrier, especially in individuals at risk of deficiency or with recurrent gastrointestinal manifestations.

The association between zinc, immunity, and diarrhea is particularly important in HIV, because intestinal changes can worsen malabsorption of nutrients, increase systemic inflammation, and impair immune recovery. Thus, zinc emerges as a micronutrient of clinical interest, not only for its immunomodulatory function, but also for its relationship with intestinal health and with the reduction of associated morbidities.

Vitamin D, CD4 Recovery, And virologic failure during ART

Vitamin D stood out in studies conducted in the era of antiretroviral therapy. Sudfeld et al. investigated adults starting ART in Tanzania and found an association between vitamin D and HIV progression, suggesting that low levels of this micronutrient may be linked to worse clinical outcomes during treatment [18]. This finding is relevant because it shifts the discussion of the micronutrient deficiencies do context exclusively pre-ART for the contemporary scenario of chronic HIV management.

Havers et al. expanded this evidence by demonstrating that insufficiency and deficiency of 25-hydroxyvitamin D were associated with disease progression and virologic failure after the initiation of antiretroviral therapy in different population settings [19]. This finding indicates that vitamin D may be related not only to immune recovery, but also to relevant virologic outcomes.

Complementarily, Ezeamama et al. observed that vitamin D deficiency impaired the rate of CD4+ T lymphocyte recovery in HIV-positive adults using HAART [20]. This finding reinforces the hypothesis that vitamin D may influence immune reconstitution, especially in individuals who have incomplete CD4 recovery despite antiretroviral treatment.

Multivitamin Supplementation and Adjuvant Interventions

Clinical trials with multivitamins showed

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important, especially in contexts prior to the universalization of ART. Fawzi et al. demonstrated that multivitamin supplementation in women living with HIV was associated with delayed disease progression and reduced adverse outcomes [16]. In a previous study, the same group assessed vitamins in pregnant women infected with HIV-1 and observed effects on pregnancy outcomes and T-cell counts [17].

Baum et al., in a clinical trial conducted in Botswana, assessed multivitamin and selenium supplementation in asymptomatic adults infected with HIV and not yet exposed to ART, investigating whether the intervention could delay disease progression [14]. These findings are relevant to understanding the historical role of nutritional supplementation in periods when the initiation of antiretroviral therapy was later.

However, systematic reviews indicate that micronutrient supplementation in people living with HIV should be interpreted with caution. Visser et al., Irlam et al., and Okoka et al. pointed out that the effects vary according to the micronutrient, the population, the presence of ART, the dose used, and the outcomes assessed [1-3]. Thus, supplementation should be considered as a strategy complementary, preferably guided by nutritional and laboratory assessment, and not as a substitute or alternative to antiretroviral treatment.

Table 1. Synthesis of the Main Findings of the Studies Included in the Review

Thematic axis	Related studies	Main micronutrients	Population/context	Main outcomes observed	Scientific interpretation
HIV deficiencies and progression	[4-9]	Vitamin A, Vitamin B12, multiple micronutrients	Adults living with HIV, including pre-ART populations and vulnerable groups	Clinical progression, immune decline, wasting, and mortality	Deficiencies can act as markers of clinical severity and possible cofactors of a worse prognosis
Selenium and disease progression	[11,12,15]	Selenium	Pregnant women and adults living with HIV	Disease progression, mortality, viral load, and CD4	Selenium has biological plausibility through its antioxidant and immunological role, but effects vary depending on the population
Zinc and	[10,13]	Zinc	Adults living with	Failure	Zinc can

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Thematic axis	Related studies	Main micronutrients	Population/context	Main outcomes observed	Scientific interpretation
immunity			HIV, including patients in HAART/TARV	immunological, diarrhea, and persistence of nutritional deficiency	contribute to immune function and integrity intestinal, especially in individuals at nutritional risk
Vitamin D and response to TARV	[18-20]	Vitamin D, 25-hydroxyvitamin D	Adults starting or using TARV/HAART	Virological failure, clinical progression, and Lower CD4 recovery	Vitamin D stands out as a marker associated with immunological and virological response during TARV
Multivitamin supplementation	[1-3,14,16,17]	Multivitamins, vitamins B, C, E, selenium, zinc, and vitamin D	Adults, women, and pregnant people living with HIV	Clinical progression, mortality, immunological parameters, and pregnancy outcomes	Supplementation may have benefit in specific contexts, but it should not be generalized without an individualized assessment

The results show that the relationship between micronutrients and HIV is complex and influenced by multiple factors. In studies conducted before modern ART, nutritional deficiencies showed a strong association with disease progression and mortality. In the era of ART, the most relevant findings involve the persistence of deficiencies in treated patients, the association of vitamin D with virological failure and incomplete CD4 recovery, as well as the possible adjunctive benefit of zinc, selenium, and multivitamins in selected contexts

selected [3,10,12-14,18-20].

Therefore, the synthesis of the studies suggests that evaluating micronutrients may have clinical importance in the follow-up of people living with HIV, especially in patients with low immunological recovery, gastrointestinal symptoms, anemia, food insecurity, weight loss, higher inflammatory burden, or risk of treatment failure. However, the methodological heterogeneity of the studies, differences between populations, and the historical change in access to ART require cautious interpretation of the

results and reinforce the need for individualized assessment and intervention strategies nutritional.

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DISCUSSION

The findings of this integrative review show that micronutrient deficiencies in people living with HIV represent a clinically relevant, multifactorial phenomenon that remains present even in the era of antiretroviral therapy. Although ART has significantly transformed the prognosis of infection, reducing morbidity and mortality and enabling sustained control of viral replication, the studies analyzed indicate that nutritional factors continue to influence clinical progression, immune recovery, and therapeutic response in different population contexts [1,3,10,18-20].

The reviewed literature suggests that micronutrient deficiencies may act in two complementary dimensions. The first refers to their role as **markers of clinical severity**, since reduced levels of vitamins and minerals may reflect a worse nutritional status, greater systemic inflammation, the presence of opportunistic infections, poor intestinal absorption, weight loss, or more advanced disease. The second dimension involves their possible participation as **pathophysiological cofactors,**considering that micronutrients such as vitamin A, vitamin B 12, vitamin D, zinc, and selenium perform essential functions in immunity, the antioxidant response, epithelial integrity, hematopoiesis, and inflammatory regulation [4-7,10,18-20].

In this sense, the relationship between micronutrients and HIV progression should not be interpreted in a linear way. Nutritional deficiency may be a consequence of the chronic infection itself, but it may also worsen the immunological and metabolic mechanisms involved in disease progression. People living with HIV frequently present conditions that favor this cycle, such as low food intake, increased metabolic demand, chronic diarrhea, persistent inflammation, intestinal changes, and greater consumption of antioxidants. Thus, micronutrient deficiency can be part of a set of factors that contribute to immunological and clinical deterioration, especially in individuals who are nutritionally vulnerable [4,5,10].

Among the micronutrients assessed, vitamin A was one of the first to be associated with mortality and progression

HIV clinic. Classic studies by Semba et al. indicated that vitamin A deficiency was related to an increased risk of death in individuals infected with HIV, especially when associated with wasting [8,9]. This finding is consistent with the role of vitamin A in maintaining mucosal integrity and in the cellular immune response. However, it is necessary to consider that these studies were conducted in contexts prior to the widespread availability of ART, which limits direct extrapolation to the current therapeutic scenario. Still, they remain relevant to understand the role of nutritional impairment as a prognostic marker in people living with HIV.

Vitamin B12 was also shown to be important in the reviewed literature. Tang et al. observed an association between low serum concentrations of vitamin B12 and faster progression of HIV-1 infection [7]. This result is clinically plausible, since vitamin B12 is involved in hematologic, neurologic, and immunologic processes. In people living with HIV, deficiency of this micronutrient may be influenced by insufficient intake, poor absorption, and alterations gastrointestinal and persistent inflammatory status. However, as with vitamin A, the available findings require caution, since B12 deficiency may be both a contributing cause and a consequence of more advanced disease.

Selenium stood out as a micronutrient of interest due to its role in antioxidant defense and immune modulation. The Kupka et al. cohort showed an association between low selenium status and accelerated disease progression in pregnant women living with HIV-1 [11]. In addition, the Hurwitz et al. clinical trial observed that selenium supplementation was associated with suppression of viral load progression and with favorable indirect effects on CD4 counts [12]. These data suggest that selenium may be relevant at the interface between oxidative stress, viral replication, and immune function.

Despite this, evidence on selenium should not be interpreted as a universal indication for supplementation. The Kupka et al. trial in pregnant women showed that effects may vary according to the population and outcomes assessed [15]. In addition, differences in baseline nutritional status, the administered dose, the stage of disease, in the

access to TARV and socio-economic conditions can substantially modify the results. Therefore, selenium can be considered a micronutrient of clinical interest, but its supplementation should be discussed as intervention adjuvant, individualized and dependent on nutritional and laboratory assessment.

Zinc showed a relevant association with immune function, intestinal integrity, and gastrointestinal morbidity. The study by Jones et al. showed that micronutrient deficiencies may persist in patients on HAART, reinforcing that antiretroviral therapy does not completely eliminate the risk of nutritional changes [10]. In contrast, the clinical trial conducted by Baum et al. demonstrated that zinc supplementation was associated with a reduction in immune failure and the occurrence of diarrhea in adults living with HIV [13].

These findings are particularly important because diarrhea and intestinal dysfunction can perpetuate a cycle of poor absorption, inflammation, and nutritional deficiency. Zinc is involved in maintaining the intestinal barrier, cellular differentiation, and the innate and adaptive immune response. Thus, its deficiency may contribute to greater vulnerability to infections, poorer absorption of nutrients, and less efficient immune recovery. However, as with other micronutrients, supplementation should consider the patient's baseline status, since inadequate or unnecessary doses may not produce clinically relevant benefit.

In the contemporary era of ART, vitamin D has emerged as one of the most prominent micronutrients. Studies by Sudfeld et al., Havers et al., and Ezeamama et al. showed an association between low levels of 25-hydroxyvitamin D, clinical progression, virologic failure, and lower recovery of CD4+ T lymphocytes in adults initiating or using ART/HAART [18-20]. These findings indicate that vitamin D deficiency may be related not only to overall nutritional status, but also to the immune response during treatment.

The importance of vitamin D in HIV can be explained by its role in modulating innate and adaptive immunity, regulating inflammatory cytokines, and mounting a response against infectious agents. In people living with HIV, its deficiency may be influenced by low sun exposure, inadequate diet, chronic inflammation,

coinfections, metabolic changes, and possible interactions with therapeutic regimens. The association with virological failure observed by Havers et al. broadens the discussion, as it suggests that vitamin D status may be linked to relevant therapeutic outcomes, although it is not possible to establish definitive causality from observational studies [19].

Incomplete CD4 recovery in individuals with viral suppression is a recognized clinical challenge in routine HIV care. In this context, vitamin D deficiency may be a potentially modifiable factor, especially in patients with poor immune reconstitution despite appropriate ART. The study by Ezeamama et al. strengthens this hypothesis by associating vitamin D deficiency with lower CD4 recovery in adults receiving HAART [20]. However, well-designed clinical trials are needed to confirm whether correcting deficiency results in consistent improvements in immunological and virological outcomes.

Another relevant point concerns the role of multivitamins. The trials conducted by Fawzi et al. indicated that multivitamin supplementation was associated with delayed disease progression, improvement in immunological parameters, and benefits in specific populations, especially women and pregnant people living with HIV [16,17]. Similarly, Baum et al. evaluated combined supplementation with multivitamins and selenium in asymptomatic adults not receiving ART, contributing to understanding the role of these interventions in settings prior to the universal and early initiation of antiretroviral therapy [14].

However, the interpretation of these studies requires historical contextualization. Many trials with multivitamins were conducted before the current guidelines for early ART initiation were established. In that setting, supplementation could delay clinical progression in individuals who had not yet been treated. Today, ART must remain the central and irreplaceable axis of HIV care. Nutritional supplementation may be useful as a complementary strategy, especially in individuals with proven deficiency, higher nutritional risk, or unsatisfactory immune recovery, but it should not be presented as a therapeutic alternative to antiretroviral treatment [1,3,14,16].

The systematic reviews included in this analysis reinforce this cautious interpretation. Visser et al. showed that micronutrient supplementation in adults living with HIV has variable and not always consistent effects on mortality and disease progression [1]. Irlam et al. noted that, in children living with HIV, the effects also depend on the type of micronutrient, the population, and the outcomes evaluated [2]. Meanwhile, when analyzing adults on ART, Okoka et al. indicated that zinc and vitamin D may support immune recovery in certain contexts, whereas selenium and vitamin E may contribute to preventing anemia [3]. Thus, the best reading of the evidence is not universal supplementation, but an individualized assessment of nutritional status.

The methodological heterogeneity of the studies is one of the main limitations of the literature. The studies differ regarding design, population, stage of infection, presence or absence of ART, type of supplement, dose, intervention duration, baseline nutritional status, and outcomes analyzed. In addition, an important part of the observational evidence does not allow causal inference, because low levels of micronutrients may reflect the themselves severity of the disease. Thus, the association between deficiency and worse prognosis does not mean that necessarily, that supplementation will correct all clinical outcomes.

Another important aspect is the difference between pre-ART and post-ART contexts. Older studies remain relevant for understanding the relationship between nutrition and HIV progression, but their findings should be reinterpreted in light of current treatment. Early initiation of ART, the greater efficacy of modern regimens, reduction of viral load, and better clinical follow-up have profoundly changed the scenario in which nutritional supplementation is assessed. Currently, the role of micronutrients appears to be more appropriately suited as part of an integrated approach to care, aimed at correcting deficiencies, supporting immune function, improving quality of life, and preventing nutritional complications [3,10,18-20].

From a clinical standpoint, the results of this review support the importance of periodic nutritional assessment in people living with HIV, especially those with low CD4 counts, incomplete immune recovery, anemia, chronic diarrhea,

weight loss, food insecurity, coinfections, or therapeutic failure. A investigation laboratory of micronutrients can be particularly useful when there are clinical signs consistent with deficiency or when the patient presents an unfavorable course despite cART. In this context, supplementation should be targeted, monitored, and integrated into the overall therapeutic plan.

The discussion also highlights an important gap: there is still a need for contemporary studies conducted in populations using modern cART regimens, with baseline assessment of micronutrients, adequate control of confounders, and clinically relevant outcomes. Future clinical trials should clarify whether correcting specific deficiencies, such as vitamin D, zinc and selenium can consistently improve CD4 recovery, reduce virologic failure, decrease persistent inflammation, or improve quality-of-life markers.

Therefore, the evidence analyzed indicates that micronutrient deficiencies in HIV have clinical and scientific relevance, but they should be understood within a multifactorial model. Disease progression and the response to ART are influenced by viral, immunologic, metabolic, nutritional, social, and therapeutic factors. In this scenario, assessing and correcting nutritional deficiencies represent a potentially useful strategy, provided they are applied in an individualized, evidence-based manner, and always as a complement to treatment antiretroviral.

CONCLUSION

The evidence analyzed in this integrative review shows that the deficiencies of micronutrients represent a relevant clinical factor in the context of HIV infection, especially due to their association with disease progression, mortality, immunologic failure, incomplete recovery of CD4+ T lymphocytes, virologic alterations, anemia, diarrhea, and increased vulnerability to infectious complications. Although antiretroviral therapy has transformed the prognosis of people living with HIV, studies indicate that viral suppression does not completely eliminate the nutritional, metabolic, and inflammatory risks associated with the disease [1,3,10,18-20].

Among the micronutrients assessed, vitamin A, vitamin B12, vitamin D, zinc, and selenium stood out as the most frequently associated with adverse clinical and immunological outcomes. Vitamin A was associated with mortality and wasting, vitamin B12 with faster progression of infection, selenium with clinical progression and viral load, zinc with immunological failure and diarrhea, while vitamin D showed an important relationship with virological failure and lower CD4 recovery during ART [6-13, 18-20].

The findings also suggest that micronutrient supplementation may have benefits in specific contexts, especially when there is proven deficiency, nutritional vulnerability, low immunological recovery, or an increased risk of complications. Clinical trials with zinc, selenium, and multivitamins have demonstrated potential favorable effects on immunological parameters, viral load, diarrhea, anemia, and clinical progression. However, systematic reviews emphasize that the results are heterogeneous and depend on the type of micronutrient, dose, population, baseline nutritional status, stage of disease, and use of ART [1-3, 12-16].

In this way, supplementation should not be interpreted as a universal intervention or as a substitute for antiretroviral therapy. Its most appropriate role is as a complementary, individualized strategy based on clinical, nutritional, and laboratory assessment. The integrated approach to a patient living with HIV should consider not only viral suppression, but also nutritional status, the presence of specific deficiencies, the quality of immune recovery, the risk of therapeutic failure, and the social conditions that interfere with ongoing care.

It is concluded that micronutrient deficiencies can act both as markers of severity and as possible cofactors involved in the progression of HIV and the incomplete response to ART. Periodic assessment of nutritional status—especially in individuals with low CD4 counts, anemia, chronic diarrhea, weight loss, food insecurity, coinfections, or unsatisfactory immune recovery—can contribute to more comprehensive and effective care.

Finally, it is recommended to develop new studies

contemporary ones, especially trials

randomized clinical trials and prospective cohorts in populations using modern ART regimens, to clarify with greater precision the impact of correcting specific deficiencies on immune recovery, virologic failure, persistent inflammation, quality of life, and morbidity and mortality in people living with HIV.

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