Chapter

Malnutrition in HIV/AIDS: Aetiopathogenesis

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Abstract

HIV/AIDS can cause malnutrition directly and also indirectly through opportunistic infections (OIs). Infectious diarrhoea and tuberculosis are the commonest OIs linked to malnutrition in HIV/AIDS. Environmental enteric dysfunction has now been identified to play a significant role in HIV-malnutrition. Food insecurity is bidirectionally associated with aggravation and perpetuation of HIV infection. Increasingly, drugs used in antiretroviral therapy have been recognised to lead malnutrition in many ways. Both HIV and malnutrition are most prevalent in the poorest areas of the world, and there is a convergence of etiological factors. Malnutrition depresses every aspect of immune function. Deficiency of key micronutrients like iron, folic acid, zinc, selenium and vitamins A, C and D also adversely affects immune function. Recent research has led to a greater understanding of these mechanisms. Immune dysfunction secondary to malnutrition is referred to as nutrition-associated immunodeficiency. Hence it is easy to surmise that malnutrition and HIV/AIDs are a deadly duo.

Keywords: HIV/AIDS, malnutrition, immunity, environmental enteric dysfunction

1. Introduction

HIV/AIDS and malnutrition form a deadly duo with each one fuelling the other. Malnutrition increases susceptibility to infection by causing immune dysfunction in manifold ways. The depressed immune status can amplify HIV replication and accelerate progression of HIV disease to AIDS. Malnutrition increases the risk of death on initiation of ART in PLHA, and untreated HIV/AIDS puts individuals at risk for malnutrition. The same is more acute in infants and children under 5 years of age [1, 2]. Untreated or advanced HIV/AIDS is again associated with a compromised immune status that makes these patients susceptible to opportunistic infections. Of these, tuberculosis is the most common and most debilitating one. Apart from TB, common infections like pneumonia, kala-azar, meningitis and malaria are also more common in these patients. Infections and the chronic low-grade inflammatory state perpetuated by HIV infection suppress appetite, increase catabolism of muscles and push patients towards malnutrition. Loss of strength means low earning capacity and loss of livelihood. The social stigma of HIV fractures social and family bonds. All of them further push patients towards impoverishment and malnutrition.

2. Magnitude of the problem

A study in 2010 estimated that more than 925 million people in the world were undernourished and one-third of the global disease burden could be eliminated by adequate nutrition [3]. The greatest burden of malnutrition is seen in the age group of 2–5 years. According to 2014 data, 159 million children were stunted and 50 million were wasted [4]. Among different geographic regions, South Asia and sub-Saharan Africa have the highest global burden of malnutrition. In 2014, they accounted for 25.1 and 32% of stunted children under 5 years of age, respectively [5, 6]. Sub-Saharan Africa suffers from a high burden of undernutrition, affecting 23.2% of its population, and in 2015 this region accounted for 69% of the estimated people living with HIV globally. A review of case records of 4350 children aged 2 – 19 years enrolled in HIV-care programme in Benin, Burundi, Cameroon, Chad, Cote d'Ivoire, Mali and Togo was done in 2011. The mean age was 10 years (IQR 7 – 13). Anthropometric indices that were measured were height-for-age z-score (HAZ) and weight-for-height z-score (WHZ) for children < 5 years and BMI-for-age z-score (BAZ) for children >5 years. All values were expressed as z-scores. About 80% of the children were on ART for a median period of 36 months. The prevalence of malnutrition was 42% (95% CI 40–44%). About half of all children in the age group of 2–5 were malnourished, and among children in the age groups of 5–10 and 10–19, the prevalence was 36 and 44%, respectively. The authors then subtyped malnutrition as acute, chronic or mixed. Acute malnutrition was defined as WHZ/BAZ < −2SD and HAZ ≥ −2SD. The prevalence of acute, chronic and mixed malnutrition was 9 (95% CI 6–12%), 26 (95% CI 23–28%) and 7% (95% CI 5–10%), respectively. Acute malnutrition was associated with age < 5 years, male sex, severe immunodeficiency and absence of ART. Chronic malnutrition was most common in children <5 years (37%). The prevalence of chronic malnutrition in the age groups 5–10 and 10-19 years was 24% each. Mixed malnutrition was associated with male sex, age < 5 years, severe immunodeficiency and recent initiation of ART (<6 m) [7]. In another study from Ethiopia, malnutrition was seen in 224 of the 372 children with HIV/AIDS (60.2%). Of all the malnourished children, 67.7% were males and 52.7% were females. In the age group of 2–5 years, 96.3% were malnourished, and in the age groups of 5–10 and 10–15 years, it was 48.3 and 59.2%, respectively [8].

In a study from North India, 56.7% of 102 HIV-positive children presenting to an ART clinic had protein-energy malnutrition (PEM). Children with higher grades of PEM had lower CD4 cell counts [9]. Of the 4105 children initiating ART in TREAT Asia Paediatric HIV Observational Database (TApHOD) cohort, 355 (11.9%) had severe malnutrition (defined as baseline weight-for-height z-score of <−3 if aged 6–60 months or BMI-for-age z-score of <−3 if aged 61 months to 14 years) [10]. This is very high compared with the estimated prevalence of severe malnutrition in the general paediatric population in SE Asia (5.2%) [11]. The risk factors for severe malnutrition were age 6–12 months, male sex and prior diagnosis of tuberculosis [10].

Among adult patients, moderate malnutrition is more common than severe malnutrition. A study done in Salvador, Brazil, looked at prevalence of malnutrition in PLHA in the age group of 20–59 years. One hundred twenty-seven patients were enrolled in the study. Malnutrition (BMI < 18.5 kg/m^2) was found in 55 (43%) of the subjects and severe malnutrition (BMI < 16 kg/m^2) in 15%. Lean body mass and fat body mass were lower than the fifth percentile of a reference population in 80 (63%) and 38 (30%) patients, respectively [12]. Another study from Iran compared malnutrition among adults with HIV/AIDS with the general population. One hundred PLHA were enrolled in the study. Mild (BMI 17–18.4 kg/m^2), moderate (BMI

16–6.9 kg/m^2) and severe malnutrition (BMI < 16 kg/m^2) were seen in 24, 38 and 15%, respectively. Except for mild malnutrition, all the other figures were significantly higher than that for the general population [13]. Data from the Nutrition for Healthy Living (NFHL) cohort in Boston, USA, reveals some disturbing facts about HIV-malnutrition in the era of HAART. The total prevalence of HIV-associated weight loss and wasting in the cohort was 38%. Both weight loss and wasting were seen in those who were on a robust ART regimen, those who had failed ART and those who were ART-naive. The authors also found that the prevalence of weight loss and wasting had not changed over time and that it was as frequent in 2005 as it had been in 1997 [14].

3. Impact of HIV-malnutrition: mortality and morbidity

Malnutrition contributes to increased mortality among children, mainly due to infections. Children with severe acute malnutrition had 12 times the risk of dying when compared with well-nourished children of the same age [15]. HIV infection further increases the risk of dying among children with malnutrition. A systematic review and meta-analysis of 17 studies on 4891 children with severe acute malnutrition in sub-Saharan Africa revealed that children with HIV infection were more likely to die than those not infected with HIV (30.4 vs. 8.4%, P < 0.001, relative risk 2.81, 95% CI 2.04–3.87) [16]. Non-immunological factors also contribute to increased mortality among children with malnutrition. These include impaired respiratory excursions due to reduced muscle mass predisposing to chest infections, reduced electrolyte absorption from the gut, impaired renal concentration capacity which puts the child at risk for dehydration and lastly impaired cardiac function that can cause heart failure [17]. The NHFL study showed that for every 1% increase in weight loss since the previous visit, the risk of death rose by 11%. When weight loss was >10% below the baseline weight, the relative risk of death increased nearly sixfold [14].

4. Aetiopathogenesis of HIV-malnutrition

4.1 HIV infection per se and HIV wasting syndrome

HIV wasting was included as an AIDS-defining criterion (ADC) in 1987 by the Centers for Disease Control and Prevention (CDC). HIV wasting is defined as an involuntary weight loss of >10% from the baseline and associated with diarrhoea, fever or weakness of ≥30 days duration in the absence of a concurrent illness. HIV wasting is associated with disease progression and death even when patient is on effective ART [18]. Wasting is associated with low serum albumin levels and deficiency of important micronutrients like zinc and selenium [13].

The primary cause for weight loss in PLHA is inadequate calorie intake. One of the key factors leading to this is anorexia secondary to elevated levels of pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). These cytokines also cause a rise in total daily energy expenditure (TEE) due to an increase in resting metabolic rate (RMR) or resting energy expenditure (REE) [19, 20]. RMR may increase by 10–30%, more so in the presence of concurrent infections or high viraemia and increased catabolism of proteins [14, 21–25]. Macallan et al. evaluated patients with HIV/AIDS for TEE, REE and energy intake. The REE was 9.6% higher in HIV-infected men than in HIV-negative men (25.0 vs. 22.8 kcal/kg/d; p = 0.002). But the mean TEE in HIV-infected men was lower than that of the population standard for HIV-negative men between

30 and 39 years of age (2750 kcal/d versus 3420 kcal/d) The authors concluded that this was due to reduced physical activity. However, there is a net negative energy balance because reduced TEE does not offset decreased energy intake due to anorexia and malabsorption [19]. Roubenoff and colleagues showed that cytokines released from activated PBMCs like TNF-α and IL-1β independently predicted loss of lean body mass and changes in REE [26]. And, nutritional and metabolic abnormalities correlated better with cytokines from PBMCs than plasma cytokines. Levels of TNF-α and IL-1β and IL-6 from PBMCs were better than plasma cytokines in distinguishing between participants with or without HIV wasting [27].

4.2 Anorexia

Various causes of anorexia leading to HIV wasting include oral candidiasis, oesophageal candidiasis, CMV oesophagitis, fever and tuberculosis. ART is also associated with significant adverse effects that include anorexia. Many NRTIs cause mitochondrial toxicity. Lactic acidosis and pancreatitis are two of the most serious effects of mitochondrial toxicity due to NRTIs, especially didanosine, stavudine and zidovudine. Frank lactic acidosis is not common, but hyperlacticacidaemia is fairly common and is seen in about 15% of patients on these NRTIs. It manifests with anorexia, nausea, weight loss, peripheral lipoatrophy and mildly deranged transaminitis. Zidovudine causes anorexia, nausea and fatigue in 5–10% patients during the early stages of therapy. Other drugs associated with anorexia and nausea include ritonavir and elvitegravir-cobicistat combination [28, 29]. Anorexia may also be secondary to jaundice secondary to HBV/HCV coinfection. Many ART drugs can cause hepatitis by different mechanisms. NRTIs cause steatohepatitis by mitochondrial toxicity. This usually develops after 6 months of treatment. NNRTIs cause hepatitis by hypersensitivity reaction. This usually occurs within the first 2–4 months of therapy. Protease inhibitors may cause hepatitis especially with HBV or HCV confection by an unknown mechanism. Anti-tubercular therapy is also another significant cause of iatrogenic hepatitis. Alcoholism, drug abuse and depression may all be associated with anorexia.

4.3 Chronic diarrhoea

Diarrhoea remains a common complaint among PLHA and adversely affects quality of life. In the early years of the HIV epidemic, HIV wasting syndrome was a common presentation, especially in sub-Saharan Africa. It would often be associated with prolonged diarrhoea (>30 days duration). Causes for diarrhoea can be infectious and non-infectious. In most of the low-income countries, the aetiology continues to be infectious, and etiologic agents differ according to geographical region [30, 31]. The aetiological agents can be broadly grouped as protozoa, bacteria, fungi and viruses.

4.3.1 Infectious diarrhoea

Cryptosporidium parvum is the most frequently identified protozoan causing chronic diarrhoea in PLHA universally [32]. In developing countries, prevalence rates of cryptosporidium infection can be as high as 20% [33]. The high prevalence is due to sewage/faecal contamination of water sources [34]. Although cryptosporidium is commonly associated with chronic diarrhoea in HIV-positive persons, it can also cause cholera-like explosive diarrhoea and intermittent acute and relapsing illnesses. Microsporidia (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*) are other important protozoa causing diarrhoea in AIDS patients [35–38]. In a study from New York, microsporidia were found in 39% of AIDS patients undergoing

gastrointestinal evaluation for diarrhoea [39]. But this high prevalence is uncommon in other parts of the USA and the rest of the world [36]. *Isospora belli* is an endemic gastrointestinal pathogen among PLHA in Haiti, but it is uncommon in the USA [36, 37]. The widespread use of trimethoprim-co-trimoxazole prophylaxis for *Pneumocystis carinii* may be the reason for this low prevalence: *Isospora* being very susceptible to trimethoprim-sulphamethoxazole. Cyclospora have also been identified in HIV-infected patients with chronic diarrhoea in low- to middle-income countries (LMIC) [35–37]. Amoebic dysentery or invasive amoebic disease like liver abscess or amoeboma is not more common in PLHA than in the general population even in developing countries. A high frequency of stool carriage in asymptomatic homosexual men is however common [30]. Stool carriage of amoebae in PLHA includes *E. dispar*, *E. hartmanni*, *E. coli* and also non-pathogenic *E. histolytica* [40]. There is no difference in the prevalence or severity of giardiasis among PLHA and HIV-negative populations.

The spectrum of bacterial pathogens causing diarrhoea in HIV-infected patients is similar to that in the general population. *Salmonella*, *Shigella*, *Campylobacter* and *E. coli* remain the commonest causes of diarrhoea in PLHA also. The immunocompromised state can lead to a symptomatic carriage of *Shigella* and *Campylobacter* [30]. *Clostridium difficile* should be actively excluded in patients with recent history of antibiotic therapy [41]. Clostridial infection is more common in severely immunocompromised patients (CD4+ T-cell count <50/ mm^3). *Mycobacterium avium* complex (MAC) typically causes diarrhoea in patients with AIDS with profound immunosuppression (i.e. CD4+ T-cell count <50 cells/mm^3) [42]. Features of systemic involvement in the form of fever and weight loss often accompany diarrhoea [43]. MAC usually involves the small intestine; however, it can affect the entire GI tract [44, 45].

Fungi are rare etiologic agents for diarrhoea in HIV-infected. The only exception is histoplasmosis which can infect all parts of the GIT; can cause fever, weight loss and diarrhoea; and may require hospitalisation [46].

Cytomegalovirus (CMV) was identified in as many as 45% of GI biopsies in AIDS patients with diarrhoea in a study from France [47]. CMV infection usually presents late in the natural history of HIV/AIDS, occurring when CD4 count is <100 cells/mm^3. In contrast, CMV was not detected in any of the rectal biopsies from 29 African patients with chronic diarrhoea and abnormally appearing rectal mucosa [48]. Other viruses that have been identified in stools of PLHA with chronic diarrhoea include adenovirus, rotavirus, astrovirus, picornavirus and coronavirus [49, 50]. An Italian study followed up a cohort of 50 HIV-negative and 10 HIV-positive children for 1 year and collected stool samples from the children every alternate week. The samples were tested for rotavirus (RV), and they found that while HIV-positive children shed more RV in stools, these rotaviral infections were not more often associated with diarrhoea than in HIV-negative children [51]. Similar prevalence was also reported from Lusaka in Zambia and Baltimore in the USA [52, 53].

Chronic *Strongyloides* infection may be present as chronic diarrhoea. *Strongyloides* hyper-infection can occur in the immunocompromised. Disseminated *Strongyloides* infection leads to migration of larvae into various tissues outside the gut. The migrating larvae carry gut bacteria along, leading to bacterial translocation which can trigger systemic inflammation and sepsis [54].

4.3.2 Non-infectious diarrhoea

4.3.2.1 ART-induced diarrhoea

With early diagnosis and institution of antiretroviral therapy, the incidence of infective diarrhoea has declined, and non-infectious causes are being increasingly identified. The common causes now are ART-associated diarrhoea, HIV enteropathy

and causes seen in the general population. About 60% of patients receiving ART gave history of diarrhoea in the previous month [55]. Data from clinical trials suggest that up to 19% of these events may have been due to the adverse effects of ART [56]. Among the ART drugs, protease inhibitors (PIs) seem to be most strongly associated with diarrhoea. In mouse models, PIs and reverse transcriptase inhibitors significantly increased water and electrolyte secretion into intestinal lumen *in vivo* [57]. Rufo and colleagues demonstrated that protease inhibitors in general, and nelfinavir in particular, potentiate signalling through muscarinic and calcium-dependent receptors of intestinal cells leading to increased chloride secretion into the lumen [58]. Stool samples of these patients also had increased concentrations of sodium and chloride consistent with secretory diarrhoea. In an *in vitro* study, Bode and colleagues showed that PIs induced apoptosis of human intestinal epithelium, thereby compromising barrier function and increasing water secretion in gut lumen. Decreased alkaline phosphatase activity in cells exposed to PIs led to accumulation of unfolded proteins in the cytosol. A failure of the cell's 'unfolded protein response', a specific signalling pathway aimed at returning the cell's protein folding function back to normal, triggered cellular apoptosis [59]. Wu and colleagues found that lopinavir and ritonavir induced endoplasmic reticulum dysfunction in intestinal epithelial cells that led to diarrhoea [60].

4.3.2.2 HIV enteropathy

HIV enteropathy is an idiopathic form of diarrhoea observed in all stages of HIV disease in the absence of an infectious source and with characteristic histologic features [61–63]. Changes include crypt epithelial proliferation leading to increased crypt height, later crypt cell encroachment onto villi and relative decreased villous height. The consequence of these changes are diarrhoea and malabsorption [64, 65]. While the exact mechanisms by which these changes occur in the GI tract are unclear, HIV has been postulated to alter signalling and cellular structure, which may lead to architectural distortion [61]. Keating and colleagues investigated monosaccharide absorption in patients with HIV and AIDS. They demonstrated that patients with diarrhoea had significant malabsorption of all monosaccharides tested [66]. Malabsorption occurred irrespective of pathogen-positive or pathogen-negative diarrhoea, indicating that HIV had an independent direct role. This may be due to the ability of HIV to infect mucosal epithelial cells [67]. Increased mucosal infiltration by activated CD8+ T cells results in high levels of pro-inflammatory cytokines which can directly damage the mucosal barrier [61, 63]. Other hypotheses for the mechanism of HIV enteropathy include decreased transepithelial electrical resistance, decreased sodium-dependent glucose absorption and increased intercellular permeability in HIV-infected cells [68]. HIV enteropathy can also lead to malabsorption of vitamin B_{12}, bile acid and monosaccharides [61, 64, 68].

4.4 Environmental enteric dysfunction

Chronic diarrhoea, water, sanitation and hygiene (WASH) have been implicated as causative factors for severe stunting in low- and middle-income countries for a long time. Efficacy of WASH interventions in reducing diarrhoea and malnutrition has been lower than expected. This led to the search for another cause. Today, there is sufficient evidence that the cause is environmental enteric dysfunction (EED). It is 'an apparently seasonal and reversible disorder characterised by gut mucosal cell villous atrophy, crypt hyperplasia, increased permeability and increased inflammatory cell infiltrate'. The principal driver of EED is the high

burden of intestinal infectious disease which is not enough to cause diarrhoea but enough to induce a state of chronic immune activation in the gut mucosa, thereby leading to epithelial damage. Dysbiosis of gut microbiota is also now considered to have an important role. The pathogenesis is probably chronic exposure to pathogens leading to a T cell-mediated immune response in the gut which continues to remain in an inflammatory hyperimmune state. This exaggerated immune response leads to structural changes in the gut mucosa, increased inflammation and permeability of the intestines, resulting in disrupted gut immune response; reduced absorption, delivery and utilisation of nutrients; and finally nutritional deficiency. There are also features of systemic inflammation, microbial translocation (MT) across the permeable gut mucosa and changes in the gut microbiome. Malnutrition further impairs the renewal of gut mucosal cells, maturation and proliferation of intestinal cells and pancreatic islet cells. The chronic low-grade inflammation inhibits endochondral ossification, thus inhibiting bone growth and leads to stunting [69].

The pathological hallmark of EED is villus blunting, which means that in histological sections villus height is reduced and villus width increased. Increased intestinal permeability can be detected using disaccharide probes. This is considered a diagnostic hallmark of EED. In adults confocal laser endomicroscopy (CLE) can be used to detect leakage of fluorescein dye from systemic circulation into the gut lumen. In adults with EED, CLE shows extensive leakage into the gut lumen occurring especially at the villous tips. This suggests that micro-erosions secondary to disordered epithelial cell shedding may be an important cause for the increased permeability [70]. The increased permeability leads to malabsorption of nutrients and also microbial translocation (MT) from the lumen into systemic circulation via gut mucosa. This MT is also important in perpetuating a chronic inflammatory state. Due to MT, some important biomarkers of MT are now being used to detect EED. These include bacterial cell wall lipopolysaccharide (LPS), soluble lipopolysaccharide co-receptor (sCD14) and antibodies to the LPS core antigen (EndoCAb) [71]. The clinical impact of EE, apart from stunting, is decreased immunological response to oral vaccines.

Does EED fuel HIV replication and disease progression? It is attractive to think it does so. Aggregation of intraepithelial lymphocytes and lamina propria T-cell populations has been described in children with EED. The T cells expressed CD69 and HLA-DR. Children with EED had 4–5 times more CD3+ T cells and 15–30-fold higher number of CD25+ T cells in the lamina propria than the UK controls. They also had a higher proportion of T cells than TCRαδ+ [72]. Activated lymphocytes in a milieu rich in inflammatory cytokines would be the perfect ground for HIV attachment and replication. However there have been no studies to prove or disprove this. But Jacob and his colleagues have demonstrated that the dominant effect of HIV on enteric mucosa is to increase villous crypt depth [73]. Hence HIV and EED may work synergistically to aggravate malnutrition.

4.5 Oral ulcers

Recurrent and severe oral ulcers make eating uncomfortable and painful. Decreased food intake over a period of time can precipitate malnutrition. Oral candidiasis is the most frequent oral disease associated AIDS, with a prevalence of 70–90% [74–76]. It often occurs early in the course of the disease. With decline in immune status, its frequency and severity worsens, and it may occur along with oesophageal candidiasis. Recurrent major aphthous ulcers and herpetiform aphthous ulcers are painful and adversely affect food intake. Other conditions like Kaposi sarcoma are becoming uncommon now.

4.6 Tuberculosis

Coinfection with HIV and *Mycobacterium tuberculosis* (TB) is an extremely common problem. TB is the largest single cause of death in HIV-positive individuals, and, in areas of high prevalence, it is the most common coinfection in HIV-positive children. HIV and TB pathogens interact, resulting in an accelerated clinical course and premature death. TB infection results in secondary wasting. Indeed, weight loss is the presenting feature in almost 50% of cases of TB, and persistent anorexia is a feature in approximately one-quarter. Swaminathan, Padmapriyadarsini and colleagues studied the nutritional status of HIV-positive subjects with TB (n = 174) and HIV-positive ones without TB (n = 488). They compared their nutritional status to that of HIV-negative people of the same socioeconomic status (n = 160). They found that 50% of HIV-positive subjects with TB and one-third of HIV-positive subjects without TB had a BMI of <18.5 kg/m^2. Moreover, HIV-positive subjects both with and without TB had lower mid-arm circumference, hip circumference and waist circumference than HIV-negative individuals. HIV-positive people with TB remained underweight even after adequate treatment for TB underscoring the negative impact of TB on the nutritional status of these people and also the synergistic effect of HIV-TB confection in aggravating malnutrition [77]. Furthermore, malnutrition is a risk factor for the acquisition of primary TB infection, as well as progression to active disease [78–80]. Other infections—particularly pneumonias, which are very common in HIV-positive children—have also been found to contribute to the increased risk of malnutrition in children in several lower-income countries.

4.7 HIV endocrinopathies

Adrenal insufficiency is the commonest endocrinopathy in the HIV-infected. The mechanism of primary adrenal insufficiency in the HIV-infected is twofold: HIV adrenalitis and adrenal gland destruction secondary to tuberculosis, CMV or other opportunistic infections [81]. Sepsis may also precipitate acute adrenal insufficiency. Adrenal insufficiency can also be iatrogenic, triggered by drugs like ketoconazole and rifampicin [82]. Secondary adrenal insufficiency can be due to the direct effect of HIV on the hypothalamic-pituitary-adrenal (HPA) axis also. Cytokines like interleukin-1 (IL-1), IL-6 (in a synergistic manner) and TNF-α can suppress the HPA [83]. HIV-positive patients who develop adrenal insufficiency may present either acutely or chronically. Acute insufficiency manifests in the critically ill as Addisonian crisis characterised by profound hypotension. In our study on hypoadrenalism in the HIV-infected with current or past tuberculosis, it was found that certain clinical features occurred consistently. They included history of fatigue, lethargy, muscle weakness, low mood/irritability, significant weight loss and need to micturate frequently and findings of hypotension, both resting and postural and pale skin (under publication). The prevalence of hypoadrenalism in HIV and HIV-TB varies from 20 to 70%. This is mainly because many studies were only done on critically ill patients in the hospital. The use of standard and low-dose ACTH stimulation test also made a difference in pickup. Nevertheless, wasting in an HIV-positive patient should trigger a search for adrenal insufficiency. On the other hand, in one study it was seen that testosterone deficiency does not lead to significant wasting [26].

4.8 Co-trimoxazole prophylaxis (CPT)

Severe acute malnutrition (SAM) contributes to 1 million childhood deaths annually worldwide, and its treatment is a key strategy for reducing childhood mortality [84]. Infectious disease is thought to be the main mediator of mortality

in children with SAM. Trehan and colleagues studied the efficacy of empirical antimicrobial therapy in children with severe acute malnutrition but without clinical features of infection. Two thousand seven hundred sixty-seven children in the age group of 6–59 months were randomised into three arms. One received oral amoxycillin, the other cefdinir and the last group a placebo for 7 days. Twelve-week mortality rates for the three groups were 4.8, 4.1 and 7.2%, respectively. The relative risk for death for placebo compared with amoxycillin was 1.55 (95% CI 0.7–2.24) and for placebo compared with cefdinir was 1.80 (95% CI 1.22–2.64). Differences in mortality and recovery were not statistically different between the amoxycillin and cefdinir arms [85].

Daily co-trimoxazole prophylaxis reduced all-cause mortality and hospital admissions in children with HIV/AIDS. This was despite high levels of antimicrobial resistance being identified in vitro among invasive isolates at study sites [86, 87]. Co-trimoxazole protected HIV-infected children against malaria, pneumonia and sepsis [88]. Other studies have shown its role in preventing recurrent urinary tract infections, pneumonia in children with measles and infections in children with specific immunodeficiencies [89–91]. Prendergast and colleagues reported that co-trimoxazole prophylaxis retards decline in weight and height for age in HIV-infected children, not on ART [92]. Boettiger and colleagues also found that CPT may enhance weight recovery in children with malnutrition on ART [10]. In both HIV-infected and malnourished children, the beneficial effect of antimicrobial therapy is primarily due to prevention and treatment of infections. Other collateral benefits could be reduction of inflammation which would reduce diversion of nutrients and decreased cytokine-mediated growth retardation and also reduced enteropathy and perturbations of gut flora [93].

4.9 Substance abuse and psychiatric disorders

HIV infection and chronic drug abuse both compromise nutritional status. There is a synergistic effect in HIV-positive drug users that leads to wasting and significantly impacts mortality. Illicit drug use may interfere with nutrient absorption, mute appetite and alter metabolism. Lifestyle of chronic drug users may compromise their access to food, food selection, housing, family and social support [94]. Use of injection drugs correlated with lower protein intake in the NFHL cohort study [14]. IV drug can be associated with HIV-HBV or HIV-HCV coinfections. Patients with hepatitis frequently lose weight and develop anaemia and neutropenia. As liver disease advances, anorexia, dietary intolerance and limitation of nutrient intake occur [95, 96]. AIDS-related dementia and neuropsychiatric disorders can cause malnutrition as the ability of patients to care for themselves is compromised. Many may forget to eat and others may be unable to prepare balanced meals [97].

4.10 Socioeconomic factors

4.10.1 Food insecurity

Wasting and malnutrition in HIV-positive children is not only due to the HIV disease or opportunistic infections. It is also due to breakdown of family structure and the failure of social and healthcare systems. Food insecurity is defined as a lack of access to sufficient, safe and nutritious food to meet dietary needs and maintain a healthy and active life [98]. Another way of defining it is 'insufficient quantity or quality of food, reductions of food intake, and feelings of uncertainty, anxiety, or shame over food' [99].

There is a high prevalence of food insecurity among PLHA. An American study reported that about 50% of PLHA on ART in San Francisco, Atlanta and Vancouver were food insecure [100, 101]. In the NFHL cohort from Boston, 36.1% participants were classified as 'food insecure' [14]. A study done in Senegal compared the prevalence of food insecurity among general population and PLHA in two different regions of Senegal: Dakar where the predominant source of income was nonagricultural business and Ziguinchor in Casamance province where it was agriculture. The prevalence of food insecurity among PLHA in the two regions was much higher being 84.6 and 89.5%, respectively, than in the general population (16–60%). The prevalence of severe food insecurity was 59.6 and 75.4% in Dakar and Ziguinchor, respectively [102]. Similar findings are reported from both urban and rural settings in other parts of Africa. Among 898 PLHA on ART in Kinshasa, Democratic Republic of Congo, 57% of the people were food insecure and 50.9% were severely food insecure [103]. The prevalence is higher in other studies. In one from Windhoek, Namibia, 92% of 390 PLHA on ART were food insecure, and 67% were severely food insecure [104]. In a big study involving 76,038 HIV-infected people in Western Kenya, the prevalence of food insecurity ranged from 20 to 50% [105]. The prevalence of food insecurity in rural Uganda and North Ethiopia were 74.5 and 40.4%, respectively [106, 107].

Food insecurity is linked to lower educational levels and low socioeconomic status, unemployment, larger household size and number of children [108, 109]. Andrade and colleagues found that daily per capita income correlates well with malnutrition in Salvador, Brazil. They found that for daily per capital incomes of <US$ 2, US$ 2–4.99 and US$ 5–9.99, the prevalence of malnutrition increased by 2.01 (95% CI 1.06–3.81), 1.75 (95% CI 0.92–3.35) and 1.42 (95% CI 0.76–2.65) times, respectively, compared to the patients whose *per capita* household income was US$ ≥10.00 per day [12]. The presence of even one HIV-positive person in a family pushes the family to food insecurity in Africa [110]. In most of Africa, South America and Asia, women are the primary caregivers in households. They procure foodstuffs, gather firewood, prepare food and feed the children. Not surprisingly, the risk of malnutrition in children increases if the mother has HIV/AIDS. Timely provision of ART to HIV-positive women reduces under-5 mortality rates to those similar to children of HIV-negative women.

HIV/AIDS is a major factor leading to food insecurity. The disease leads to debility of family members in the prime of their life. This leads to loss of jobs, reduced productivity and increased caregiver burden. In turn, food insecurity has many adverse effects on health and well-being of PLHA. It leads to risky coping strategies in households with HIV-positive individuals. Wages get directed to purchase of ART, and many family members may exchange sex for money or food, thereby putting themselves at higher risk of acquiring HIV infection and STDs. It also increases risk of vertical transmission of HIV by risky infant-feeding practices. It increases non-adherence to ART, aggravates adverse effects of ART, and leads to incomplete viral suppression, worsening health and increased mortality [111, 112]. In DRC and Namibia, food insecurity was associated with increased odds of poor adherence to ART (adjusted odds ratio 2.06 and odds ratio 3.84) [103, 104].

4.10.2 Poor weaning practices.

Mothers' level of education influences occurrence of malnutrition in children. Poor education leads to lack of awareness of the importance of exclusive breast feeding for the first 6 months of the infant's life, failure to introduce complementary feeds at 6 months and limited food diversity. It also contributes to adherence to local taboos with regard to refraining from giving foods of animal origin to children.

In addition, lack of access to food supplements for HIV-positive children also contributes to malnutrition among these children in many parts of Africa [113]. Exclusive breast feeding during first 6 weeks of life resulted in consistently higher z-scores for weight at 52 weeks of age in HIV-infected infants than in those on only top feeds or mixed feeds (difference of 130 g for male children and 110 g for female children) [1].

5. Pathobiology of immunodeficiency in malnutrition

Malnutrition is considered to be the commonest cause of immunodeficiency in the world. It adversely impacts every aspect of immune function. All these immune dysfunctions are collectively referred to as nutritional-acquired immunodeficiency syndrome (NAIDS). Understanding of malnutrition-related immunodeficiency can shed a lot of insight into immunodeficiency of HIV/AIDS.

Profound thymic atrophy with depletion of thymocytes and changes in thymic extracellular matrix are seen even in moderate malnutrition. It is however difficult to say whether these changes in thymic function are due to malnutrition *per se* or due to the severe infections frequently associated with malnutrition. Changes in thymic micro-environment like decreased thymic epithelial cells, expansion of extracellular matrix and decreased production of thymic hormone all contribute to thymic depletion. Thymocyte depletion results from increased apoptosis of CD4 and CD8 double-positive, double-negative and single-positive (immature) thymic lymphocytes. Apoptosis is driven by increased circulating levels of glucocorticoids, reduced leptin levels and deficiency of dietary protein and zinc.

Bone marrow cellularity is reduced, its stroma altered and there is limitation of extra-cellular matrix expansion. A study on bone marrow changes in children with PEM showed erythroid hypoplasia/dysplasia in the marrows of 50% children with kwashiorkor, 30% children with marasmic-kwashiorkor and 28.5% children with marasmus [114]. Suppression of cell cycle progression of haematopoietic progenitor cells with cell cycle arrest in G0/G1 phase is seen in protein malnutrition. This results in reduction in red cell and white cell lineages. In addition, bone marrow granulocytes display impaired blastic response to granulocyte-colony stimulating factor (G-CSF) and suboptimal mobilisation on lipopolysaccharide challenge. In protein-deficient mice models, bone marrow mesenchymal cells tend to differentiate into adipose cells, thereby altering the cytokine micro-environment in the bone marrow and compromising haematopoiesis. Despite this, the total number of leucocytes in peripheral blood of children with severe acute malnutrition remains normal. However, the number of dendritic cells is reduced [115]. Mice with transferrin receptor-1 deficiency are unable to absorb adequate iron. This results in impaired T-cell development and fewer mature B cells [116].

Secondary lymphoid tissue in the spleen and lymph nodes shows similar degenerative and hypo-proliferative changes in mouse protein-deficient models. The spleen has a thickened capsule and is deficient in splenocytes and splenic mononuclear cells. Cell cycle arrest, similar to that seen in the bone marrow, is seen. Splenic white pulp is also disorganised. Changes in lymph nodes can be seen even in moderate malnutrition. Zinc and iron deficiencies exaggerate changes caused by protein-energy malnutrition. There is hypoplasia of lymph nodes, decreased number of dendritic cells, macrophages, neutrophils and fibroblasts. The ability of lymph nodes to act as an effective barrier to pathogen spread is compromised. Poor trafficking of soluble antigens through the lymphoid conduits is also seen.

It would be intuitive to assume that like all other lymphoid tissue, the gut-associated lymphoid tissue (GALT) should also be hypoplastic in malnutrition. This has not been shown in humans conclusively.

5.1 Innate immune system dysfunction in malnutrition

Malnutrition affects the primary physical defensive barrier of the body. Thinning of dermis and reduced collagen levels are seen in animal models of PEM. In marasmic mice, thinning of the epidermis, with decreased hydration of stratum corneum, and decreased epidermal proliferation are seen. Wound healing is delayed and there is delayed wound contraction. Increased infiltration of wound site with inflammatory cells, decreased laying down of collagen, oedema of the extracellular matrix and altered neovascularisation are seen. Though skin changes like oedema and 'flaky paint dermatosis' and desquamation are common in kwashiorkor, there is no definite clinical proof to associate these changes with decreased immunity.

The changes in gut mucosa are more dramatic and have greater clinical consequences. These have been discussed above in environmental enteric dysfunction. At this juncture it suffices to say that gastric acid secretion is decreased in severe malnutrition, and gut permeability to bacteria is increased. In the oral cavity flow of saliva is reduced. Vitamin A deficiency reduces differentiation of epithelial cells in the skin, cornea and respiratory, urogenital and gastrointestinal tracts. This compromised epithelial barrier makes bacterial and viral invasion easy. Retinoic acid deficiency can alter gut mucosal barrier function. There is a marked reduction of type 3 innate lymphoid cells (ILC3) in gut mucosa of mice with vitamin A deficiency resulting in decreased production of IL-17 and Il-22 and increased susceptibility to bacterial infections. Concomitantly, there is an expansion of type 2 innate lymphoid cells (ILC2). These cells secrete IL-13 which causes goblet cell hyperplasia, increased mucus production and an increased resistance to gut helminths. Zinc reduces biofilm formation and decreases expression of virulence and adherence factors of entero-aggregative *Escherichia coli*. This may be one of the reasons for frequent diarrhoeal illnesses in malnourished children. A double-blinded randomised placebo controlled trial on zinc supplementation in children between the ages of 6 and 30 months in Delhi showed reduction in frequency, severity and duration of diarrhoea disease in the zinc-supplemented group [117].

Acute-phase reactant synthesis seems unaffected by malnutrition. C-reactive protein (CRP) rise is similar in normal and malnourished children when faced with an infectious challenge [118]. In contrast the so-called negative phase reactants like transferrin, pre-albumin, fibronectin and α2-HS glycoprotein are consistently decreased in malnutrition and do not rise adequately during an infectious challenge [119]. Complement levels are decreased in severe malnutrition. This is due to reduced synthesis in the liver and also increased consumption in the periphery. This is most marked in kwashiorkor. Reduction in C3 levels in malnutrition has been consistently reported from other studies as well [120].

As it has already been mentioned, there is no reduction in the total number of leucocytes in the peripheral blood. But chemotaxis and microbicidal activity of neutrophils are decreased in children with PEM. This may partly be due to decreased lysosomal enzyme synthesis and reduced glycolytic activity. Vitamin A is important for neutrophil maturation. Neutrophils in retinoic acid-deficient mouse models show impaired chemotaxis, phagocytosis and generation of reactive oxygen species. Vitamin A deficiency also decreases number and function of NK cells. Vitamin C deficiency in animals decreases apoptosis of neutrophils and results in their decreased clearance. Vitamin C deficiency exaggerates inflammation and retards its resolution in mouse model of sterile inflammation. Administration of vitamin C attenuates lung, kidney and liver injury in murine models of intra-abdominal sepsis and lethal LPS administration. The salutary effects of vitamin C in the lung include reduced pro-inflammatory response, increased epithelial barrier

function, increased alveolar fluid clearance and decreased coagulopathy. Zinc modulates respiratory bursts in neutrophils. Moderate to severe malnutrition does not lead to reduction in absolute number of natural killer (NK) cells in children, but their function is depressed. Iron deficiency impairs macrophage function. Intracellular iron activates nuclear factor kB (NF kB). NfkB is responsible for exerting a restraint on reactive oxygen species and c-Jun-N-terminal kinase (JNK) signalling. These signalling pathways are crucial for antagonism of programmed cell death (PCD) induced by pro-inflammatory cytokines. Hypoxia-inducible factor-1α (HIF-1α) is an iron-dependent transcription factor that promotes synthesis of antimicrobial peptides by macrophages. Hence iron deficiency can lead to apoptosis of macrophages and also blunt their anti-microbial activity [121, 122].

Folate deficiency in rats is associated with reduced number of neutrophils and eosinophils. Zinc regulates release of pro-inflammatory cytokines like IL-1β, IL-6 and IFN-α by innate immune cells, and its deficiency leads to reduced synthesis of Th-1 cytokines. Selenium exerts its antioxidant activity via selenoproteins. They regulate pro-inflammatory mediators via mitogen-activated protein kinase and peroxisome proliferator-activated receptor-γ. Genetic knockout of selenoprotein genes in mice leads to impaired migration of macrophages and neutrophils and reduced phagocyte oxidative burst. Vitamin D plays a crucial role in macrophage function. Its deficiency increases risk of active TB and also increases risk of relapse of TB in both HIV-uninfected and HIV-positive individuals. The primary action of vitamin D is exerted via the vitamin D receptors on macrophages. There is a supplementary action via toll-like receptor signalling. Vitamin D leads to increased production of cathelicidin and β2-defensin which increase secretion of pro-inflammatory cytokines, induce anti-tuberculous autophagy and restrict growth of mycobacteria inside macrophages [123].

In severe malnutrition, dendritic cell numbers are reduced in peripheral blood and in lymphoid tissues. A study from Zambia showed reduced numbers of DCs and also impaired DC maturation and impaired ability of DCs to stimulated T-cell proliferation in the face of endotoxaemia. The DC function normalised with nutritional therapy [115]. Murine models with deficiency of protein, iron and zinc have shown reduction in number resident DCs in lymph nodes. These DCs also showed dysregulation of DC chemoattractants during inflammation. PEM grossly impairs antigen-presenting capacity and T-cell activation ability of DCs. Vitamin A, as retinoic acid, is vital for DC function. When there is inflammation, retinoic acid accelerates maturation and antigen-presenting capacity of DCs. Dendritic cells also store and release retinoic acid to act on other immune cells. Vitamin D plays an important role in regulation of DC function and exerts an anti-inflammatory role. It retards DC maturation, antigen presentation and T-cell priming.

5.2 Malnutrition and adaptive immune system

Malnutrition does not affect the total number of lymphocytes in peripheral blood. The total levels of immunoglobulins IgG and IgM in blood and secretory IgA in duodenal fluid and urine are unaltered. When malnutrition in children is compounded by a severe respiratory or intestinal bacterial infection, the number of B cells is reduced when compared to infected but well-nourished children. B lymphocyte function is preserved in PEM, but the profile of secreted immunoglobulins (Igs) and specific antibody-mediated immune responses are altered. Levels of Th1-type immunoglobulins (IgG2a and IgG3) are unaltered, those of tTh2-type Igs (IgG1 and IgE) are raised and those of secretory IgA are reduced. Severe protein malnutrition leads to decreased levels of secretory IgA in tears and saliva. Zinc deficiency depletes cells of B-cell lineage in the bone marrow. Vitamin A-deficient

mice show a poor IgG response which is reversible by vitamin A supplementation. Vitamin A-deficient mice also have decreased number of IgA-secreting plasma cells in their Peyer's patches [123, 124].

Levels of CD4+ and CD8+ cells in peripheral blood remain unaltered in malnourished children hospitalised with serious infections. But there is a decrease in the number of CD4+ CD45RO+ memory T cells and effector T cells (CD4+ CD62L− and CD8+ CD28−) in severe malnutrition. Th1 cytokines required for Th1 differentiation (IL-7, IL-12, IL-18 and IL-21) and function (IL-2 and IFN-γ) are reduced in peripheral blood mononuclear cells of children with malnutrition and severe infection. In the same children, an overexpression of Th2 cytokines (IL-4 and IL-10) and increased apoptosis of CD3+ T cells is noted. The ability of T cells to respond to an inflammatory stimulus is also altered. There is an impaired antigen-specific T-cell response (decreased CD8+ cells and decreased IL-2 production by CD4+ cells), but antigen-specific antibody production is unimpaired. Proliferative response to phytohaemagglutinin is reduced. Delayed-type hypersensitivity response is also impaired in severe malnutrition. Zinc is required for Th1 differentiation and Th1 responses. It increases expression of IL-2, IFN-γ and IL-2Rb β2. Zinc deficiency therefore results in a reduction of CD4/CD8 ratio and levels of Th1 cytokines. Selenium deficiency adversely affects CD4+ T-cell proliferation, activation and function. The production of IL-2 and expression of IL-2 receptor are both reduced, and there is impaired mobilisation of calcium. Retinoic acid acts on naive T cells and promotes expression of gut-homing receptors, differentiation into Th2 phenotype and T-regulatory cells especially in the gut mucosa. It also inhibits maturation to Th1 phenotype or Th17 cells. RA activates B cells in mucosa and GALT to transform into IgA+ antibody secreting cells (ASC). Hence RA deficiency can seriously impair gut mucosal immunity. Due to its influence on effector T-cell function, vitamin A deficiency can lead to inadequate immune response to some vaccines. Vitamin A supplementation has been shown to lead to 20–30% reduction in all-cause mortality and reduction of incidence and severity diarrhoea diseases and measles [125, 126].

The effect of HIV infection on immune systems mirrors that of malnutrition in most aspects with just a few key differences. Natural killer cell activity and complement activity are increased in HIV infection. There is an increased secretion of pro-inflammatory cytokines (IL-1β, TNF-α, INF-γ and IL-6, IL-8 and soluble IL-2 receptors) and reduction of anti-inflammatory cytokines (IL-1 receptor antagonist, IL-4, IL-10 and IL-13). The chronic inflammatory state is also a hypercatabolic one and leads to increased mobilisation of amino acids from skeletal muscles that are further used for gluconeogenesis in the liver. TNF-α and IFN-γ also suppress appetite leading to decreased food intake. Hypercatabolism and decreased diet lead to malnutrition and HIV wasting. The combination of HIV and malnutrition aggravates reduction of CD4 and CD8 T cells, impairs bactericidal function of neutrophils and macrophages, impairs delayed-type hypersensitivity response and blunts antibody response to immunisation [97].

HIV infection also has a direct impact on nutrition. Studies have shown that among asymptomatic HIV-positive children, the rates of protein, carbohydrate and fat malabsorption are 30–60, 32 and 30%, respectively [127, 128]. Increased protein turnover occurs to cater for proliferation of neutrophils, fibroblasts and lymphocytes, production of immunoglobulins and acute-phase reactants and increased urinary nitrogen loss. This mainly comes from increased skeletal muscle breakdown and increased hepatic protein synthesis. Other metabolic changes that occur include elevated hepatic fatty acid synthesis, decreased peripheral lipoprotein lipase activity, hypertriglyceridemia, increased gluconeogenesis, insulin resistance and hyperglycaemia. There is redistribution of body stores of iron and zinc, with both being mobilised to the liver. This along with inadequate dietary intake leads to iron and

zinc deficiencies. The pro-inflammatory state also leads to increased consumption of vitamins A, C and E which serve as antioxidants. There is reduction in levels of glutathione which is the principal intracellular antioxidant compound. Deficiencies of micronutrients like selenium, zinc, manganese and copper affect function of many key antioxidant enzymes. Deficiency of antioxidants leads to increased oxidative stress which triggers T-cell apoptosis and also enhances HIV replication [129].

6. Conclusion

Malnutrition depresses all aspects of immune function. HIV infection can lead to wasting and malnutrition by a complex interplay of aetiological factors. This malnutrition compounds immunodeficiency of AIDS and accelerates progression of disease and increases risk of mortality. Addressing nutrition right from the time of HIV diagnosis is a good strategy. Judicious and monitored nutritional therapy can mitigate NIADS and improve HIV clinical outcomes.

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