Food Supplementation among HIV infected adults in Sub-Saharan Africa: impact on treatment adherence and weight gain

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Abstract

Sub-Saharan Africa has the highest proportion of undernourished people in the world, along with the highest number of people living with HIV and AIDS. Thus, as a result of high levels of food insecurity many HIV patients are also undernourished. The synergism between HIV and undernutrition leads to poor treatment adherence and high mortality rates. Undernutrition has a debilitating effect on the immune system due to key nutrient deficiencies and the overproduction of reactive species (oxidative stress), which causes rapid HIV progression and the onset of AIDS. Therapeutic food supplementation used in the treatment of severe acute malnutrition is being applied to HIV palliative care; however little biochemical data exists to highlight its impact on oxidative stress and immune recovery. In addition, as most food supplements are imported by donor agencies, efforts are being put into local therapeutic food production such as the Food Multi Mix (FMM) concept to ensure sustainability. The purpose of this review is to highlight studies that examine the effectiveness of food supplementation in undernourished HIV patients in Sub-Saharan Africa; noting the parameters used to measure efficacy, as well as the long-term feasibility of supplementation.

Keywords: oxidative stress, malnutrition, HIV/AIDS, therapeutic food, FMM concept,

Introduction

According to the Food and Agriculture Organisation (FAO), the number of chronically undernourished people in the world stood at 805 million between 2012 and 2014 [1]. Undernourishment occurs as a result of an energy intake less than the amount needed for light activity and to maintain an appropriate weight in proportion to height [2]. Due to significant nutrient deficiencies, undernourished individuals, particularly children, are considerably more susceptible to acquiring infectious diseases, including HIV. Sub-Saharan Africa has the highest proportion of undernourished people in the world, with close to one in four of its population considered chronically undernourished [1]. The region was also home to approximately 24.7 million people living with HIV in 2013; accounting for nearly 70% of the global total of new HIV infections [3]. Given the increased availability of antiretroviral treatment (ART) in low-to-middle-income countries, the high prevalence of undernutrition can pose a significant hurdle to AIDS recovery; as food insecurity has been identified as a primary obstacle to ART adherence [4]. To date, ART coverage in Sub-Saharan Africa is estimated at 37%, and roughly three out of every four people currently on ART live in Sub-Saharan Africa [3].

According to WHO guidelines, nutritional support should be incorporated into HIV care alongside ART. Recommendations include an increase in energy intake of up to 50% compared to an HIV negative individual, but a normal intake of micronutrients and protein [5]. Micronutrients play important functional roles in the human immune response, however, a number of micronutrient deficiencies have been reported in HIV positive individuals. This has been linked to poor nutrient absorption due to intestinal cellular damage caused by oxidative stress.

Nutrients, Immunity and HIV infection

Micronutrients in particular antioxidant minerals such as selenium, zinc, and vitamins A, C and E play a key functional role in an active immune response [6]. For example, the antioxidant role of vitamin A and in particular its role in maintaining mucosal immunity makes it an important dietary component [7]. A function for vitamin A in enhancing T Helper Type 2 cytokine production and secretory IgA response to viral infections especially at high doses has also been reported [8]. In addition, carotenoids and other vitamin A compounds have been shown to inhibit reverse transcriptase in HIV-1 and HIV-2 [9]. Similarly, vitamin C has been shown to inhibit the HIV virus *in vitro* [10].

The combination of vitamin A deficiency and wasting have been identified as predictors of mortality in HIV disease [11]. Low zinc and iron levels have also been associated with immune abnormalities, increased susceptibility to infections and gastrointestinal malfunction with diarrhoea [12]. Such data supports the argument for micronutrient supplementation in HIV patients, however consideration must be taken as high doses of iron can induce oxidative stress, stimulate microbial growth; while excess zinc can cause HIV gene expression, multi-mineralization and integration [13, 14].

Antioxidant defence systems (ADS) are essential in limiting various reactive species (RS) from causing intestinal cellular damage [15, 16]. Immune activation can contribute considerably to the overproduction of RS at the site of infection such as the intestinal area. In HIV infected individuals who also face the double-burden of also being undernourished, the level of antioxidant protection may not be present to thwart this overproduction; which inevitably leads to oxidative stress [17]. With the onset of oxidative stress, intestinal cells can become further degraded as RS oxidize the polyunsaturated fatty acid component of membranes, disrupting cellular structure and function in the process [15]. This causes nutrient malabsorption, which is linked to wasting in HIV patients [16]. In addition, oxidative stress-related tissue damage caused during HIV infection triggers the activation of nuclear factor kappa B (NF-κB), which in turn can further enhance HIV replication [18].

The extent of oxidative damage can be determined by measuring biochemical parameters such as glutathione (GSH), glutathione peroxidase (GPx); malondialdehyde (MDA), or total antioxidant status [19, 20, 21] Glutathione has been shown to be of importance in immune function and restoration of CD4 T lymphocyte levels in HIV infection [22, 23, 24]. During an HIV infection, not only does GSH decrease but there is also an increase in oxidised glutathione (GSSG) and protein-bound glutathione (GSSP) [25]. The accompanying change in GSH:GSSG ratio indicates a change in redox status and increased oxidative stress [25]. Such oxidative stress can be exacerbated by folate deficiency, which is associated with increased production of homocysteine, a potential RS [25].

Sulphur-containing amino acids are important in metabolism and immune function, which can become depleted in the onset of protein deficiency [25]. Furthermore, should protein also be deficient there would be insufficient building blocks for glutathione synthesis (cysteine) and the methylation cycle (methionine) [25]. Cysteine and methionine are both important in the methylation cycle (crucial to folate, B_{12} and homocysteine metabolism) and the glutathione pathway [25]. Protein deficiency would also lead to biochemical (metabolic) adaptations, which

would mean various critical enzyme systems and immune globulin synthesis may become compromised [25]. The loss of lean tissue, which is a characteristic of HIV wasting, would ultimately lead to patient death.

Figure 1: the Infection – Malnutrition Cycle

HIV, Food Insecurity and Undernutrition

The synergism of HIV and undernutrition is unfortunate as one has a debilitating effect on the other, often in spite of access to ART. An HIV positive person in a food insecure household would not consume an adequate diet consisting of nutrients required for maintaining a functional immune system to prevent opportunistic infections [26].This situation usually leads to a rapid onset of AIDS, which causes a decrease in productivity due to illness and death. HIV affected households are thus more likely to experience income losses, which in turn exacerbates food insecurity and low ART adherence, as difficult situations may arise such as choices between purchasing either food or treatment [27].

As a general rule, drug adherence is difficult to achieve in an undernourished patient. Antiretroviral treatment has been shown to stimulate appetite in HIV patients, which helps with body mass recovery and improves immune function [28, 29]. Yet in a food-insecure household this may not be desirable as there would be insufficient food to satisfy a stimulated appetite. Current evidence suggests that food insecurity is a significant contributor to non-compliance with ART, and may offset the benefits of treatment. For example, HIV patients in Kenya who were offered free ART from the Medecins Sans Frontiers, cited fears of the potential side effects of taking ART on an empty stomach as a key reason for declining treatment [30]. Similarly, in Rwanda, patients interviewed listed the concern of having too much appetite without the food to fulfil it as an obstacle to maintaining adherence [4].

Considerable adverse effects have been observed in food insecure patients on ART such as hepatic toxicity [31]. In a Ugandan study, it was observed that food insecurity was heavily associated with non-adherence to ART, incomplete viral suppression and having a CD4 count less than 350 cell mm^3 [32]. This phenomenon has presented the argument for nutrition intervention to be formally introduced into HIV palliative care. Given that many HIV infected persons in low-income countries also suffer from the complications of acute to severe malnutrition, the benefits of using ready-to-use-therapeutic foods (RUTF) is being investigated among this population. Research has indicated that RUTF use is generally accepted by HIV infected persons as a means to counteract the adverse effects of ART; and

has been described as “food with medicinal qualities", making it less likely to face any cultural perceptions and practices associated with food including sharing and fasting [33].

Food Supplementation

Food intervention strategies in food-insecure countries have traditionally involved imported food rations, which are not the most financially sustainable. In Mozambique, it was estimated the cost of providing food assistance to HIV infected persons at $288 over a 3 month period, and highlighted a significant portion of costs was related to overheads such as transport [21]. Thus the local production of RUTF in food-insecure regions is being investigated, albeit on a low level. Preliminary technical guidelines are available for small and medium-scale therapeutic food production in resource-limited settings [34]. Local therapeutic food production programmes have been successfully implemented in a number of countries such as Niger, the Congo and Malawi. The majority of therapeutic foods have been designed as treatment for acute to severe malnutrition however research into how therapeutic foods can complement ART as part of HIV care is also ongoing [35]. Despite some being locally sourced, most ingredients of RUTF are either imported or donated by the World Food Programme (WFP) [36]. Thus operations remain largely unsustainable despite local production. In Malawi, the cost of local therapeutic food production was estimated at $2.60/kg, with approximately 54% of this price covering the cost of imported ingredients [35].In Kenya, a nutrient-dense therapeutic food formula using all locally-sourced ingredients was developed, piloted for taste testing and found to be well adhered to by participants [37].

Aim of Review

To date the biochemical aspect of HIV infection and its relationship with antioxidant nutrients has not often featured in nutritional intervention studies. Nevertheless, the use of food supplementation, in particular micronutrient-fortified, ready-to-use therapeutic foods (RUTF) as part of nutrition intervention strategies has gained momentum. The aim of this review is to highlight the most recent studies related to food supplementation in HIV infected adults in Sub-Saharan Africa; analysing where available, measurable outcomes such as weight gain and ART adherence with a view to providing evidence for debate on this important topic in Africa.

Selected Studies

Relevant studies were identified by a search conducted in the PUBMED database. Keywords used were "food" "HIV" "supplementation" and "intervention". The search was confined to a ten year period (2004-2014) and studies were chosen based on pre-defined inclusion/exclusion criteria. Studies were considered relevant if they measured at least two of the following outcomes including Weight/BMI, ART adherence and CD4 count. Studies were excluded if they were conducted outside of Sub-Saharan Africa, involved a non-food intervention and/or if there was either no article full-text available or the full text was not accessible free of charge. A total of ten primary studies were identified and seven met the criteria to be included in this review. Two studies were conducted outside of Sub-Saharan Africa (Haiti and India) and one study involved a non-food intervention. All seven studies (one in Zambia, two in Uganda and four in Malawi) were conducted among adults aged 18 and older (Table 1). Data extracted from each study included type of study, description of food intervention, location, duration, WHO clinical stage, sample size, and measurable outcomes. In three studies participants were described as food-insecure and in two studies participants were treatment naïve. In all eight studies participants were malnourished and/or wasted and presented with WHO clinical stage III or IV of HIV infection.

Table 1: Data from seven primary studies included in this review

Author and Date	Participant No.	Duration	Location	Supplement	Weight gain	BMI increase	ART adherence
Cantrell et al (2008)	636	11 months	Zambia	CSB	6.3 kg	N/A	High
Ndekha et al (2009)	491	3 ½ months	Malawi,	RUFS vs. CSB	5.6 kg RUFS; 4.3 kg CSB	2.2 kg/m^2 RUFS; 1.7 kg/m^2 CSB	High
Bahwere et al. (2009)	60	3 months	Malawi	Local RUTF	2.5 kg	0.8 kg/m^2	N/A
Ahoua et al. (2011)	1106	29 months	Kenya and Uganda	RUTF Plumpy'Nut ®	4 kg	1.7 kg/m^2	N/A
Oosterhout and Ndekha (2009).	593	6 ½ months	Malawi	RUFS vs. CSB	6.9 kg RUFS; 6.8 kg CSB	2.7 kg/m^2 RUFS; 2.6 kg/m^2 CSB	High
Bowie et al (2005)	360	14 months	Malawi	WFP food basket	N/A	0.46 kg/m^2	N/A
Rawat et al. (2014)	904	12 months	Uganda	WFP food basket	N/A MUAC 6.7 mm	0.6 kg/m2	N/A

CSB: Corn-soy-blend

RUFS: Ready-to-use fortified spread

RUTF: Ready-to-use-therapeutic food

WFP: World Food Programme

MUAC: Mid-upper-arm-circumference

In Zambia, approximately 54.6% of the 1.1 million people living with HIV have access to ART as of September 29th 2014 [38]. In 2013, there were approximately 27,000 AIDS related deaths [38]. A non-randomised study by Cantrell and colleagues investigated the effect of food supplementation on ART adherence in HIV adults in Zambia [39]. Food supplementation consisted of micronutrient fortified corn-soya blend (CSB) containing 6.2kg of protein; and 620ml of vegetable oil per month for each individual ration. The programme ran from May 2004 to March 2005 (11 months) and involved 636 HIV positive adults with a mean CD4 cell

count of 131cell mm^3. One hundred and thirty four (22%) of participants had a CD4 count of less than 50 cells mm^3. Three hundred and forty seven (79%) were categorised as WHO clinical stage III or IV, while 92 (21%) were categorised in clinical stage I or II.

The 411 women had a mean baseline weight of 52.9 kg, while the 218 men had a mean baseline weight of 56.1 kg. All participants were described as food-insecure. Food distribution was based on whether the patient was a primary income earner, in which case they would receive an individual ration along with additional rations sufficient for six household members. Participants classified as the "food group" began food rations in September 2004, whereas the "control group" were assigned to receive rations at a later date. ART adherence was measured within the first 12 months, according to the medication possession ratio (MPR), where the number of days late for pharmacy refills was expressed as a percentage of the total days of therapy, then subtracted from 100%. It was reported that adherence was higher in the food group compared to the control group, 70% (258/366) patients in the food group achieved an adherence of 95%, compared with 48% (79/166) in the control group. Differences in weight gain between the food and control group were 5.4kg vs. 5.1kg respectively after 6 months, and 6.3kg vs. 5.4kg after 12 months, which although not significant, was described as a "trend towards modest benefit". There was no reported increase in CD4 count in the food group compared to the control group. All food rations used in the study were donated by the WFP [39]

Approximately 46% of Malawi's HIV population of one million people were receiving ART by 2014; of which roughly 90% were adults [38]. A randomised, investigator blinded, controlled trial in Malawi reported on the effectiveness of ready-to-use fortified spread (RUFS) versus Corn-Soya-Blend (CSB) in achieving weight gain in HIV adults after 3 ½ months [39]. The study consisted of 491 HIV adults receiving ART. All participants had a BMI of less than 18.5 kg/m^2, a CD4 count of less than 250/mm3, and were categorised as WHO clinical stage III or IV. Primary outcomes included BMI and fat-free mass, while secondary outcomes included ART adherence, survival, CD4 count, HIV viral load, and quality of life. After 14 weeks, mortality rates were similar in both groups (27% in RUFS versus 26% in CSB).
There was no significant difference in ART adherence, which was high in both groups; neither was there a difference in CD4 cell count, viral load or quality of life. Participants in the RUFS group reported a 13% weight increase compared to a 10% increase in the CSB group. Fat-free mass contributed to 2.9 kg (51.8%) of the 5.6 kg weight gain in the RUFS group and 2.2 kg (51.2%) of the 4.3 kg weight gain in the CSB group. BMI increased by 2.2 in the RUFS group,

compared to 1.7 in the CSB group. In this study, the CSB was priced at US$5.40 per patient per month whereas the RUFS cost US$16.00 per patient per month, which was approximately $1 more expensive than first line ART [40].

A prospective descriptive study highlighted the effects of a locally produced ready-to-use therapeutic food (RUTF) in 60 HIV positive adults in Malawi [41]. A total of 45/60 (75%) of participants were at WHO clinical stage IV and 15 (25%) were at WHO clinical stage III. Participant eligibility included a BMI of less than 17 kg/m^2 and a middle-upper-arm circumference (MUAC) of less than 210 mm.

Participants were given 500g daily of the RUTF, which consisted of chick peas, sesame seeds, vegetable oil, sugar, maize and a micronutrient complex. This provided a daily amount of 2681kcal of energy, 61.5g protein, 24mg niacin, 2.5mg vitamin B6, 8 µg vitamin B12, 241.5mg vitamin C, and 62mg of zinc, amongst other micronutrients. Only 8 participants (13.3%) were already on triple ART including stavudine, lamivudine and nevirapine. A daily dose of cotrimoxazole (960mg) was also given to participants for the three month duration of the study. Adherence to the food supplement was measured by the number of finished pots and the measurable outcomes included MUAC, BMI, weight gain and physical activity. Out of 60 participants, 44 (73.3%) reported increases in weight, MUAC and BMI (2.5kg, 15mm and 0.8 kg/m^2 respectively). A lower BMI, MUAC and weight was observed in participants already on ART at the start of the study compared to ART naive participants. The amount of participants able to walk to the clinic increased from 25 to 47 (41.7% to 78.3%). The cost of a 500g/day ration of RUTF was valued at $45.90/person/month, which was more cost effective than other nutrition interventions including the standard food aid supplement (CSB and oil) valued at $53.25/month [41].

According to UNAIDS, Kenya has the fourth largest ART programme among low and middle income countries, although only 41% of the estimated 1.6million HIV population currently receives treatment [38]. Following close behind at fifth is neighbouring country Uganda, which had 38% of its estimated 1.6million HIV population on ART as of 2014. A retrospective cohort analysis) involved the use of RUTF originally developed for treatment of severe malnutrition such as Plumpy'Nut® and Nutriset, aimed to investigate nutritional outcome in HIV adults and to highlight the factors behind treatment failure [30]. Over a two-year period (March 2006 to August 2008) a total of 1106 malnourished adults from a Kenyan and a Ugandan HIV programme participated in the study. Participants had a median CD4 count of 114 cells/mm^3

and a BMI of less than 17 kg/m^2. A total of 617 participants were severely malnourished (55.8%), while 489 were moderately malnourished (44.2%). The amount of participants categorised in either WHO clinical stage III or IV was 705 (63.7%). Out of the 790 adults eligible for ART, 133 (16.8%) were already on treatment, while 470 (59.5%) began treatment either at the start or during the programme. A total of 187 (23.7%) participants did not receive any treatment for the duration of the study. The RUTF consisted of a micronutrient fortified, energy dense spread of peanut, milk powder, oil and sugar. Participants achieving BMI $\geq$ 18 kg/m^2 with no oedema for a minimum of two weeks were defined as "cured", based on the programme guidelines and permitted to exit the study. A total of 524 participants (47.4%) achieved this target and were discharged after a median period of 3.7 months, with a median weight gain of 8 kg (1.6g/kg/day). Forty nine participants (4.4%) were discharged as uncured after a median of 7.1 months with a median CD4 count of 292 cells/mm^3 In total, 531 participants (48.0%) failed to complete the programme, which included 250 (22.6%) whom defaulted and 132 (11.9%) whom died; both of which were severely malnourished, received nutritional treatment for less than three months, had low CD4 cell counts (96 cells/mm^3 and 36 cells/mm^3 respectively) and/or received no ART despite being eligible [42].

A retrospective study conducted in Malawi involving 593 HIV wasted adults investigated the effects of food supplementation versus no nutritional intervention [43]. Participants were previously ART naive, either WHO clinical stage III or IV, a BMI of less than 18.5 kg m^2 and CD4 count less than 250 cells/mm^3. All initiated ART upon enrolment, and were compared to a historical control group that received no supplementation but was given a dosage of cotrimoxazole prophylaxis. Outcomes were measured at the end of supplementation at 14 weeks and again at 26 weeks. Approximately half (245) of participants in the supplement group received CSB, while the remainder (244) received an RUFS; both of which were fortified with micronutrients. Higher increases of BMI were reported in the supplemented group compared to the control group. Although eight (4%) more people receiving RUFS died , it was more effective at increasing BMI and weight than the CSB, as increases of 0.5 kg m^2 and 1.2 kg respectively were observed. However, only 9% of participants receiving the RUFS supplement had a BMI that was less than 18 kg m^2. In comparison to the control group, treatment adherence improved among the supplemented group with only four people stopping ART (one on RUFS vs. three on CSB). There was no significant difference in CD4 count. The CSB supplement was priced at a monthly cost of $5USD, while the RUFS was priced at $16USD/month, which

at the time of the study was one dollar more expensive than first line ARV treatment in Malawi [43].

An observational study described the effect of food supplementation on food-insecure HIV adults needing home-based care in Malawi [43]. Food was provided to households by the World Food Programme (WFP), and contained monthly rations of 50kg maize, 5kg beans, 7.5kg 'Likuni Phala' (cereal-soya blend). Half of the households in the study also received a random allocation of 4 litres of oil, which was not strictly adhered to.

The study consisted of 360 participants, and food distribution ran for 14 months from July 2003 to September 2004. The study was divided into three periods; January 2003 to July 2003; August 2003 to November 2003, and mid-November 2003 to July 2004. Approximately 97 enrolled patients were chronically ill; up to 70% presented advanced stages of HIV infection (WHO clinical stage IV). Half of the participants were malnourished upon enrolment, with a BMI of less than 18.5kg/m^2. Mortality rate was high, as 112 (one-third) of participants died within the first four months. By the end of the study, 199 participants (56%) had died. Only 22 participants survived through all three periods. A slight increase in BMI was observed among these participants (0.49 kg/m2 per 100 days by the second survey and 0.46 kg/m2 by the third survey), but this was not significant. Participants assigned to receive oil supplements showed no significant change mean BMI, although survival was better in this group. At the time of this study, ART was not available for free in Malawi and all participants were treatment naïve.

Changes in CD4 count were not reported in this study. Although ART adherence was not specified, it was indicated that participants with increased physical activity were now able to walk to Voluntary Counselling and Testing centres and enrol in ARV programs. [44]

A prospective quasi-experimental study evaluated the impact of a WFP food basket (200g maize meal, 40g pulses, 10g vitamin A–fortified vegetable oil, 5g iodized salt, 50g micronutrient fortified CSB per person per day) provided monthly over a 12 month period (August 2008 to October 2009) to HIV adults in Uganda that were both food-insecure and ART naïve [45].

A total of 904 adults participated in the initial study, based on their eligibility to receive the WFP food basket and having a CD4 count between 200 and 450 cells/m^3; while 604 adults were part of the follow-up study. The food basket provided approximately 1100 kcal per person per day and resulted in a BMI increase of 0.6 kg/m2 and a MUAC increase of 6.7 mm. No significant association was observed between food assistance and CD4 count, however in

participants with a CD4 count greater than 350 cells/m^3, haemoglobin concentrations increased by approximately 1.0 g/dL [45].

Types of Food Supplementation

In the studies highlighted in this review, food supplementation predominantly consisted of RUTF and CSB, both of which had a high nutrient density and were developed to treat severe malnutrition. Notable differences existed between these two supplements, namely preparation methods and cost. As the RUTF did not require cooking, it was considered less likely to be shared with other household members, compared with the CSB, which was considered to be more culturally accepted. The CSB was also significantly less expensive than the RUTF.

According to Ahoua and colleagues the currently available RUTF was designed to treat paediatric malnutrition, it may not be the most suitable formulation for treatment of malnutrition in HIV infected adults **[41]**. In two studies the effect of WFP food rations were examined [43, 44]. In these studies both study populations were ART naïve, which may account for the small-to-modest increases in BMI observed (0.6 kg/m2 and 0.49 respectively). Although the food ration studies showed little to no improvement in anthropometric gains it highlighted the impact of HIV-related complications on nutritional recovery and survival. It also highlighted the ineffectiveness and lack of sustainability of food distribution programmes.

All but one study used an intervention strategy based on imported RUTF and food rations. The locally produced RUTF examined by Bahwere and colleagues performed well in improving physical activity of participants; and was more affordable than imported food supplements [41]. Studies were noted to run for relatively short durations, which was a significant limitation. The longest study was conducted over a two year period, while three studies ran between 11 and 14 months. A further three studies ran for 3 to 3 ½ months, however this was in order to limit metabolic side effects associated with ART regimens such as lipodystrophy due to the high-fat content of the RUTF supplement. Still, such a limited follow-up time was considered insufficient to fully observe the impact of the food intervention. It was also not possible to monitor the effect of access to and consumption of other food sources, which may have impacted on the results of weight gain.

Study Outcomes

Despite these limitations a key observation made in all studies was that food supplementation improved weight gain and BMI. Most notably was the 6.3kg weight increase after 12 months in participants from the study by Cantrell and colleagues [39]. Also, in all studies where it was measured, ART adherence was significantly high among participants receiving food supplementation. None of the food intervention strategies however had any significant impact on CD4 cell count in the studies where it was measured. Where measured, mortality rates were relatively high; and were largely associated with participants that were severely malnourished and ART naïve [42, 44]. These results are significant and provide justification for future study, as it highlights the important role food and nutrition security plays in improving overall quality of life for HIV patients.

A follow-up to the earlier Ndekha study by the same research group assessed the BMI of patients subsequent to food supplementation [47]. Participants were followed at three and nine month intervals after the end of the intervention trial. The initial increase in BMI was not sustained without supplementation, neither was the improvement in ART adherence and quality of life [47] The study concluded that food supplementation must be maintained throughout in order to achieve maximum nutritional gains. Clearly, this can only be achieved with a sustainable nutrition intervention programme.

Field studies involving nutrition intervention for HIV patients have generally relied on anthropometric data as primary indicators of supplementation efficacy; however the inclusion of biochemical parameters such as total antioxidant content (TAC) and lipid peroxidation can provide substantial information as to the occurrence and extent of nutrition recovery. Malondialdehyde (MDA) and 4-hydroxynonenal (HNE) are identified as lipid peroxidation end products, and plasma level measurements have been used to indicate oxidative stress occurring in the body. Oxidative stress caused by RS overproduction can be indicative of HIV infection and/or undernutrition [17]; which is linked to nutrient malabsorption and wasting in HIV patients [16]. A 1988 study showed MDA levels to be as much as 30% higher in HIV patients compared to their HIV negative counterparts [47]; whilst a study almost a decade later made similar observations in children and new-born infants [48]. None of the studies indexed in PUBMED and included in this review made an assessment of biochemical parameters.

The Food Multi-Mix Concept

409 According to the Food Multi-Mix (FMM) concept described by Zotor and colleagues, a food-
410 based approach to addressing nutritional needs for therapeutic use can be employed as a cost-
411 effective and sustainable means to improving nutrition in HIV patients [(50)]. The aim of the
412 FMM concept is to achieve affordability, sustainability and acceptance of therapeutic food
413 supplementation. The FMM concept has been previously described in its utilisation of locally
414 produced and commonly consumed foods within a community setting for clinically-based
415 interventions [(50)]. It allows for nutritional support in HIV and wasting syndromes, which is
416 aimed at replenishing energy and nutrient losses and improving weight gain. In selecting food
417 ingredients, total energy requirements including additional demands to compensate for altered
418 metabolism and special roles of nutrients including vitamin A, C, folate and minerals such as
419 zinc, selenium were all taken into consideration in accordance with specific requirements of an
420 HIV patient.

421 In various FMMs, beta carotene (vitamin A equivalent) content was on average 30% above
422 RNI values per 300 g serving. Two servings would thus provide 60% more than RNI values.
423 Apart from eggs, the carotene sources of FMMs are mostly plant-derived and are thus more
424 affordable, thus reducing the cost of meal provision. HIV patients also require additional
425 protein to ensure adequate immune system function. The consumption of 200 g of any of the
426 FMMs can provide at least two-thirds of daily protein requirements and help prevent protein
427 malnutrition, rebuild lean body mass, and assist with enzyme production. The high protein
428 content of FMMs can provide the equivalent of 143.4% RNI per serving for a 70 kg man and
429 286.8% of RNI in two servings per day. In a study conducted by Amuna and colleagues [(51)],
430 it was argued that a 70 kg adult HIV-infected male can meet at least 52.4% of his daily
431 energy requirement by consuming a 300 g serving of FMM. Regarding energy requirements,
432 two servings per day of FMM can provide between 2293 kcal (9.56MJ) and 2413 kcal
433 (10.06MJ), which is equivalent to daily requirements. This can further be enriched by adding
434 vegetable oils (rich in n-3 and n-6) and sugar where required. A typical high energy FMM
435 with energy density between 3.82-4.02 kcal/g (15.93-16.76 J/g) may thus offset the weight
436 loss resulting from abnormally excessive cytokine production e.g. TNF-$\propto$ and IL-1 [(51)].

437 The use of plant sources of oils including nuts in FMMs provide n-3 and n-6 unsaturated fatty
438 acids. The inclusion of saturated fat sources is avoided as hypertriglyceridaemia has been
439 observed in HIV patients, which can be exacerbated by ART [(52)]. Preliminary results obtained
440 in the use of FMM concept is encouraging for its application amongst HIV infected individuals
441 and warrants further investigation. Furthermore, as most areas heavily affected by HIV are

resource poor, it is anticipated that a food-based approach would acquire sustainability over time should locally based foods be utilised.

Conclusion

The nutritional and metabolic challenges of HIV/AIDS and other cachectic conditions are of increasing scientific interest. Anti-retroviral therapy and other pharmacological approaches to management continue to improve prognosis and the quality of life. However, as this review has shown, these have limited success in the absence of adequate nutritional support. Nutritional status and weight loss has been a major prognostic index of survival particularly in developing countries [46]. In countries where ART is both unavailable and inaccessible due to cost, emphasis on using foods with functional properties (nutraceuticals) as a management tool is warranted.

This review demonstrates an overall consensus that food-based intervention can play a supportive role in overall weight gain and improving ART adherence. Although BMI is seen as an important indicator of nutritional recovery, measures such as body protein repletion, increase in muscle strength, clinical improvements in appetite, and a reduced frequency of opportunistic infections can further strengthen the argument that nutritional intervention is integral to HIV palliative care. However, the biochemical processes that occur during HIV infection require a more thorough investigation. In the studies included in this review, biochemical data such as micronutrient status and lipid peroxidation were not included in either baseline or outcome measurements. In addition, as all but one intervention were based on imported food interventions, supplementation did not reflect the local diet of participants. Studies involving locally-produced food supplements, a longer follow-up time and biochemical measurements may provide more substantial information on the efficacy of nutrition intervention. The inclusion of locally/community grown crops in therapeutic food production may considerably lower both ingredient and transport costs, as well as introduce a market for small-scale community farmers. Support from government and NGOs can also assist in improving patient access to therapeutic foods. In addition, further investigation is needed into the clinical efficacy of therapeutic food formulas (including the FMM approach) given to HIV patients.

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