

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

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10 **Abstract**

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

25

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

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28

30 **Introduction**

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

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

52

53 **Nutrients, Immunity and HIV infection**

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

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

69

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

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

90 Sulphur-containing amino acids are important in metabolism and immune function, which can
91 become depleted in the onset of protein deficiency ⁽²⁵⁾. Furthermore, should protein also be
92 deficient there would be insufficient building blocks for glutathione synthesis (cysteine) and
93 the methylation cycle (methionine) ⁽²⁵⁾. Cysteine and methionine are both important in the
94 methylation cycle (crucial to folate, B₁₂ and homocysteine metabolism) and the glutathione
95 pathway ⁽²⁵⁾. Protein deficiency would also lead to biochemical (metabolic) adaptations, which

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

99

100 Figure 1: the Infection – Malnutrition Cycle

101

102 **HIV, Food Insecurity and Undernutrition**

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

111 As a general rule, drug adherence is difficult to achieve in an undernourished patient.

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

121 Considerable adverse effects have been observed in food insecure patients on ART such as
122 hepatic toxicity ⁽³¹⁾. In a Ugandan study, it was observed that food insecurity was heavily
123 associated with non-adherence to ART, incomplete viral suppression and having a CD4 count
124 less than 350 cell mm³ ⁽³²⁾. This phenomenon has presented the argument for nutrition
125 intervention to be formally introduced into HIV palliative care. Given that many HIV
126 infected persons in low-income countries also suffer from the complications of acute to
127 severe malnutrition, the benefits of using ready-to-use-therapeutic foods (RUTF) is being
128 investigated among this population. Research has indicated that RUTF use is generally
129 accepted by HIV infected persons as a means to counteract the adverse effects of ART; and

130 has been described as “food with medicinal qualities”, making it less likely to face any
131 cultural perceptions and practices associated with food including sharing and fasting ⁽³³⁾.

132

133 **Food Supplementation**

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

151

152 **Aim of Review**

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

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162 **Selected Studies**

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

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195 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 and 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/m ²	N/A

196 CSB: Corn-soy-blend

197 RUFS: Ready-to-use fortified spread

198 RUTF: Ready-to-use-therapeutic food

199 WFP: World Food Programme

200 MUAC: Mid-upper-arm-circumference

201

202 In Zambia, approximately 54.6% of the 1.1 million people living with HIV have access to ART
203 as of September 29th 2014 ⁽³⁸⁾. In 2013, there were approximately 27,000 AIDS related deaths
204 ⁽³⁸⁾. A non-randomised study by Cantrell and colleagues investigated the effect of food
205 supplementation on ART adherence in HIV adults in Zambia ⁽³⁹⁾. Food supplementation
206 consisted of micronutrient fortified corn-soya blend (CSB) containing 6.2kg of protein; and
207 620ml of vegetable oil per month for each individual ration. The programme ran from May
208 2004 to March 2005 (11 months) and involved 636 HIV positive adults with a mean CD4 cell

209 count of 131 cell mm³. One hundred and thirty four (22%) of participants had a CD4 count of
210 less than 50 cells mm³. Three hundred and forty seven (79%) were categorised as WHO clinical
211 stage III or IV, while 92 (21%) were categorised in clinical stage I or II.

212 The 411 women had a mean baseline weight of 52.9 kg, while the 218 men had a mean baseline
213 weight of 56.1 kg. All participants were described as food-insecure. Food distribution was
214 based on whether the patient was a primary income earner, in which case they would receive
215 an individual ration along with additional rations sufficient for six household members.
216 Participants classified as the “food group” began food rations in September 2004, whereas the
217 “control group” were assigned to receive rations at a later date. ART adherence was measured
218 within the first 12 months, according to the medication possession ratio (MPR), where the
219 number of days late for pharmacy refills was expressed as a percentage of the total days of
220 therapy, then subtracted from 100%. It was reported that adherence was higher in the food
221 group compared to the control group, 70% (258/366) patients in the food group achieved an
222 adherence of 95%, compared with 48% (79/166) in the control group. Differences in weight
223 gain between the food and control group were 5.4kg vs. 5.1kg respectively after 6 months, and
224 6.3kg vs. 5.4kg after 12 months, which although not significant, was described as a “trend
225 towards modest benefit”. There was no reported increase in CD4 count in the food group
226 compared to the control group. All food rations used in the study were donated by the WFP ⁽³⁹⁾

227

228 Approximately 46% of Malawi’s HIV population of one million people were receiving ART
229 by 2014; of which roughly 90% were adults ⁽³⁸⁾. A randomised, investigator blinded, controlled
230 trial in Malawi reported on the effectiveness of ready-to-use fortified spread (RUFS) versus
231 Corn-Soya-Blend (CSB) in achieving weight gain in HIV adults after 3 ½ months ⁽³⁹⁾. The
232 study consisted of 491 HIV adults receiving ART. All participants had a BMI of less than 18.5
233 kg/m², a CD4 count of less than 250/mm³, and were categorised as WHO clinical stage III or
234 IV. Primary outcomes included BMI and fat-free mass, while secondary outcomes included
235 ART adherence, survival, CD4 count, HIV viral load, and quality of life. After 14 weeks,
236 mortality rates were similar in both groups (27% in RUFS versus 26% in CSB).

237 There was no significant difference in ART adherence, which was high in both groups; neither
238 was there a difference in CD4 cell count, viral load or quality of life. Participants in the RUFS
239 group reported a 13% weight increase compared to a 10% increase in the CSB group. Fat-free
240 mass contributed to 2.9 kg (51.8%) of the 5.6 kg weight gain in the RUFS group and 2.2 kg
241 (51.2%) of the 4.3 kg weight gain in the CSB group. BMI increased by 2.2 in the RUFS group,

242 compared to 1.7 in the CSB group. In this study, the CSB was priced at US\$5.40 per patient
243 per month whereas the RUFs cost US\$16.00 per patient per month, which was approximately
244 \$1 more expensive than first line ART ⁽⁴⁰⁾.

245
246 A prospective descriptive study highlighted the effects of a locally produced ready-to-use
247 therapeutic food (RUTF) in 60 HIV positive adults in Malawi ⁽⁴¹⁾. A total of 45/60 (75%) of
248 participants were at WHO clinical stage IV and 15 (25%) were at WHO clinical stage III.
249 Participant eligibility included a BMI of less than 17 kg/m² and a middle-upper-arm
250 circumference (MUAC) of less than 210 mm.

251 Participants were given 500g daily of the RUTF, which consisted of chick peas, sesame seeds,
252 vegetable oil, sugar, maize and a micronutrient complex. This provided a daily amount of
253 2681kcal of energy, 61.5g protein, 24mg niacin, 2.5mg vitamin B6, 8 µg vitamin B12, 241.5mg
254 vitamin C, and 62mg of zinc, amongst other micronutrients. Only 8 participants (13.3%) were
255 already on triple ART including stavudine, lamivudine and nevirapine. A daily dose of
256 cotrimoxazole (960mg) was also given to participants for the three month duration of the study.
257 Adherence to the food supplement was measured by the number of finished pots and the
258 measurable outcomes included MUAC, BMI, weight gain and physical activity. Out of 60
259 participants, 44 (73.3%) reported increases in weight, MUAC and BMI (2.5kg, 15mm and 0.8
260 kg/m² respectively). A lower BMI, MUAC and weight was observed in participants already
261 on ART at the start of the study compared to ART naive participants. The amount of
262 participants able to walk to the clinic increased from 25 to 47 (41.7% to 78.3%). The cost of a
263 500g/day ration of RUTF was valued at \$45.90/person/month, which was more cost effective
264 than other nutrition interventions including the standard food aid supplement (CSB and oil)
265 valued at \$53.25/month ⁽⁴¹⁾.

266
267 According to UNAIDS, Kenya has the fourth largest ART programme among low and middle
268 income countries, although only 41% of the estimated 1.6million HIV population currently
269 receives treatment ⁽³⁸⁾. Following close behind at fifth is neighbouring country Uganda, which
270 had 38% of its estimated 1.6million HIV population on ART as of 2014. A retrospective cohort
271 analysis) involved the use of RUTF originally developed for treatment of severe malnutrition
272 such as Plumpy’Nut® and Nutriset, aimed to investigate nutritional outcome in HIV adults and
273 to highlight the factors behind treatment failure ⁽³⁰⁾. Over a two-year period (March 2006 to
274 August 2008) a total of 1106 malnourished adults from a Kenyan and a Ugandan HIV
275 programme participated in the study. Participants had a median CD4 count of 114 cells/mm³

276 and a BMI of less than 17 kg/m². A total of 617 participants were severely malnourished
277 (55.8%), while 489 were moderately malnourished (44.2%). The amount of participants
278 categorised in either WHO clinical stage III or IV was 705 (63.7%). Out of the 790 adults
279 eligible for ART, 133 (16.8%) were already on treatment, while 470 (59.5%) began treatment
280 either at the start or during the programme. A total of 187 (23.7%) participants did not receive
281 any treatment for the duration of the study. The RUTF consisted of a micronutrient fortified,
282 energy dense spread of peanut, milk powder, oil and sugar. Participants achieving BMI ≥ 18
283 kg/m² with no oedema for a minimum of two weeks were defined as “cured”, based on the
284 programme guidelines and permitted to exit the study. A total of 524 participants (47.4%)
285 achieved this target and were discharged after a median period of 3.7 months, with a median
286 weight gain of 8 kg (1.6g/kg/day). Forty nine participants (4.4%) were discharged as uncured
287 after a median of 7.1 months with a median CD4 count of 292 cells/mm³. In total, 531
288 participants (48.0%) failed to complete the programme, which included 250 (22.6%) whom
289 defaulted and 132 (11.9%) whom died; both of which were severely malnourished, received
290 nutritional treatment for less than three months, had low CD4 cell counts (96 cells/mm³ and 36
291 cells/mm³ respectively) and/or received no ART despite being eligible ⁽⁴²⁾.

292

293 A retrospective study conducted in Malawi involving 593 HIV wasted adults investigated the
294 effects of food supplementation versus no nutritional intervention ⁽⁴³⁾. Participants were
295 previously ART naive, either WHO clinical stage III or IV, a BMI of less than 18.5 kg m² and
296 CD4 count less than 250 cells/mm³. All initiated ART upon enrolment, and were compared to
297 a historical control group that received no supplementation but was given a dosage of
298 cotrimoxazole prophylaxis. Outcomes were measured at the end of supplementation at 14
299 weeks and again at 26 weeks. Approximately half (245) of participants in the supplement group
300 received CSB, while the remainder (244) received an RUFs; both of which were fortified with
301 micronutrients. Higher increases of BMI were reported in the supplemented group compared
302 to the control group. Although eight (4%) more people receiving RUFs died, it was more
303 effective at increasing BMI and weight than the CSB, as increases of 0.5 kg m² and 1.2 kg
304 respectively were observed. However, only 9% of participants receiving the RUFs supplement
305 had a BMI that was less than 18 kg m². In comparison to the control group, treatment adherence
306 improved among the supplemented group with only four people stopping ART (one on RUFs
307 vs. three on CSB). There was no significant difference in CD4 count. The CSB supplement
308 was priced at a monthly cost of \$5USD, while the RUFs was priced at \$16USD/month, which

309 at the time of the study was one dollar more expensive than first line ARV treatment in Malawi
310 ⁽⁴³⁾.

311

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

317 The study consisted of 360 participants, and food distribution ran for 14 months from July 2003
318 to September 2004. The study was divided into three periods; January 2003 to July 2003;
319 August 2003 to November 2003, and mid-November 2003 to July 2004. Approximately 97
320 enrolled patients were chronically ill; up to 70% presented advanced stages of HIV infection
321 (WHO clinical stage IV). Half of the participants were malnourished upon enrolment, with a
322 BMI of less than 18.5kg/m². Mortality rate was high, as 112 (one-third) of participants died
323 within the first four months. By the end of the study, 199 participants (56%) had died. Only 22
324 participants survived through all three periods. A slight increase in BMI was observed among
325 these participants (0.49 kg/m² per 100 days by the second survey and 0.46 kg/m² by the third
326 survey), but this was not significant. Participants assigned to receive oil supplements showed
327 no significant change mean BMI, although survival was better in this group. At the time of this
328 study, ART was not available for free in Malawi and all participants were treatment naïve.
329 Changes in CD4 count were not reported in this study. Although ART adherence was not
330 specified, it was indicated that participants with increased physical activity were now able to
331 walk to Voluntary Counselling and Testing centres and enrol in ARV programs. ⁽⁴⁴⁾

332

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

338 A total of 904 adults participated in the initial study, based on their eligibility to receive the
339 WFP food basket and having a CD4 count between 200 and 450 cells/m³; while 604 adults
340 were part of the follow-up study. The food basket provided approximately 1100 kcal per person
341 per day and resulted in a BMI increase of 0.6 kg/m² and a MUAC increase of 6.7 mm. No
342 significant association was observed between food assistance and CD4 count, however in

343 participants with a CD4 count greater than 350 cells/m³, haemoglobin concentrations increased
344 by approximately 1.0 g/dL ⁽⁴⁵⁾.

345

346

347 **Types of Food Supplementation**

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

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

362

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

374

375 **Study Outcomes**

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

386
387 A follow-up to the earlier Ndekha study by the same research group assessed the BMI of
388 patients subsequent to food supplementation ⁽⁴⁷⁾. Participants were followed at three and nine
389 month intervals after the end of the intervention trial. The initial increase in BMI was not
390 sustained without supplementation, neither was the improvement in ART adherence and
391 quality of life ⁽⁴⁷⁾. The study concluded that food supplementation must be maintained
392 throughout in order to achieve maximum nutritional gains. Clearly, this can only be achieved
393 with a sustainable nutrition intervention programme.

394
395 Field studies involving nutrition intervention for HIV patients have generally relied on
396 anthropometric data as primary indicators of supplementation efficacy; however the inclusion
397 of biochemical parameters such as total antioxidant content (TAC) and lipid peroxidation can
398 provide substantial information as to the occurrence and extent of nutrition recovery.
399 Malondialdehyde (MDA) and 4-hydroxynonenal (HNE) are identified as lipid peroxidation end
400 products, and plasma level measurements have been used to indicate oxidative stress occurring
401 in the body. Oxidative stress caused by RS overproduction can be indicative of HIV infection
402 and/or undernutrition ⁽¹⁷⁾; which is linked to nutrient malabsorption and wasting in HIV
403 patients ⁽¹⁶⁾. A 1988 study showed MDA levels to be as much as 30% higher in HIV patients
404 compared to their HIV negative counterparts ⁽⁴⁷⁾; whilst a study almost a decade later made
405 similar observations in children and new-born infants ⁽⁴⁸⁾. None of the studies indexed in
406 PUBMED and included in this review made an assessment of biochemical parameters.

407

408 **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- α 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

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

444

445 **Conclusion**

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

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

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481 coordinated the review and contributed by editing and preparing the manuscript for submission.

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