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Dietary iron intake and HIV-related outcomes among adults initiating antiretroviral therapy in Tanzania

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Abstract

Objective—Anemia is highly prevalent among people living with HIV (PLWHIV) and is often due to iron deficiency. This study evaluated the relationship of dietary iron intake levels and sources with mortality and clinical outcomes among adults initiating HAART.

Design—We conducted a secondary analysis of a multivitamin supplementation trial among 2293 PLWHIV initiating HAART in Dar es Salaam, Tanzania.

Methods—Dietary iron intake was assessed with a food frequency questionnaire at HAART initiation, and participants followed until death or censoring. Total, animal and plant-sourced iron were categorized into quartiles. Intake of food groups were categorized into 0 – 1, 2 – 3 and ≥4 servings/wk. Cox proportional models estimated hazard ratios for mortality and incident clinical outcomes.

Results—There were 175 deaths (8%). Red meat intake was associated with a lower risk of all-cause mortality (HR: 0.54; 95% CI: 0.35 – 0.83), AIDS-related mortality (HR: 0.49; 95% CI: 0.28 – 0.85) and severe anemia (HR: 0.57; 95% CI: 0.35 – 0.91), when intake ≥4 servings/wk, compared to 0 – 1 servings/wk. Legume intake was a lower risk of associated with all-cause mortality (HR: 0.49; 95% CI: 0.31 – 0.77) and AIDS-related mortality (HR: 0.37; 95% CI: 0.23 – 0.61), when intake ≥4 servings/wk, compared to 0 – 1 servings/wk. While total dietary iron and overall plant-sourced iron intake were not associated with the risk of mortality or HIV-related

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outcomes, the highest quartile of animal-sourced iron intake was associated with a lower risk of all-cause mortality (HR: 0.56; 95% CI: 0.35, 0.90) and a lower risk of AIDS-related mortality (HR: 0.50; 95% CI: 0.30, 0.90), compared to the lowest quartile.

Conclusion—Intake of iron-rich food groups may be associated with a lower risk of mortality and critical HIV-related outcomes among adults initiating HAART.

Keywords

dietary iron; anemia; iron deficiency; food groups; HIV/AIDS; wasting; mortality; antiretroviral therapy; food frequency questionnaire

Introduction

Remarkable gains have been achieved in reducing global mortality related to the human immunodeficiency virus (HIV) due to expanded access to highly active antiretroviral therapy (HAART [1]). The primary contributors to this decline have been fewer new HIV infections, and improved HIV treatment access and effectiveness [2, 3]. Globally, 67% of people living with HIV (PLWHIV) were on HAART by 2019[3]. Nevertheless, mortality remains high in many African countries, with 7 – 13% of PLWHIV dying within the first year of HAART initiation [4-6].

Anemia is common among PLWHIV and worsens the risk of all-cause mortality, incident pulmonary tuberculosis (PTB), and disease progression[7, 8]. It results from systemic inflammation, poor dietary intake, micronutrient deficiencies and use of some antiretroviral agents[8-13]. Iron deficiency (ID) accounts for 20 – 44% of anemia among PLWHIV[11, 14-16] and results from inadequate intake or absorption of dietary iron [11, 14-16]. Iron is an essential micronutrient required for cellular metabolism, immune function, and other biological processes[12, 17]. There are currently no guidelines for preventing or treating ID among PLWHIV[18] due to concerns that intervening to improve iron stores may worsen viral replication and mortality risk [11, 19, 20]. Dietary intake among PLWHIV has not been well studied, and the relationship of dietary iron intake and HIV-related outcomes is unclear.

This study aimed to examine the relationship of the total, animal-, and plant-sourced dietary iron and the intake of iron-rich food groups on the incidence of mortality, PTB, severe anemia, and weight loss. This nutritional data provides a unique opportunity to evaluate the hypothesis that dietary iron intake is protective against mortality and adverse HIV-related clinical outcomes.

Methods

Study Design and Population

We conducted a secondary analysis of existing data from a randomized trial conducted from 2006 to 2009 in Dar es Salaam, Tanzania (www.clinicaltrials.gov identifier: NCT00383669). The parent study aimed to demonstrate whether daily oral high-dose vs. standard-dose multivitamin supplements (containing vitamins B complex, C, and E) reduced the risk of HIV disease progression or death among PLWHIV initiating HAART [21]. High-dose

supplements contained 2 to 21 times the recommended dietary allowance (RDA) for the vitamins, while the standard-dose supplements contained the RDA. The trial supplements did not contain iron. PLWHIV aged ≥18 years intending to stay in Dar es Salaam for two years were eligible. Pregnant and lactating women were excluded. HAART initiation was limited to World Health Organization (WHO) HIV disease stage IV, CD4 cell count <200 cells/μL or stage III with CD4 cell count <350 cells/μL[22]. First-line HAART were nevirapine (NVP) or efavirenz (EFV), in combination with any two of stavudine (d4T), lamivudine (3TC), and zidovudine (AZT). Participants received cotrimoxazole prophylaxis when CD4 was under 200cells/μL and were treated for opportunistic infections according to national guidelines. Hemoglobin testing was done before HAART initiation as part of routine clinical assessment. The trial did not have any eligibility criteria related to hemoglobin testing. Participants who died in the first 30 d of HAART initiation were excluded in the present analysis.

Measurement of dietary intake

Dietary intake was assessed using a semi-quantitative 119-item food frequency questionnaire (FFQ) interview-administered by trained health workers within 45 days of HAART initiation. The FFQ has been shown to perform moderately well among urban-dwelling Tanzanian adults[23, 24]. Participants were asked if they had consumed the foods in the previous 30 days, and if so, how often. Then, the frequencies were converted to servings per day using Food Exchange lists that were derived from household diet surveys in Tanzania[25]. Intake of total energy and nutrients were calculated using the Tanzania Food Composition Tables [25]. The dietary iron component of each food item was summed to obtain total dietary iron, plant-sourced iron, and animal-sourced iron. Food items considered as animal-sourced were red meat (beef, goat and pork), poultry, fish, liver, eggs and dairy. Food items considered as plant-sourced included vegetables, legumes, nuts, cereal, tuber, fruits, beverages and sweets. Participants that did not have an FFQ interview completed in the 45 d after HAART initiation and those with extreme total energy intakes of <800 kcals or >5000 kcals were excluded due to improbable values.

Iron-rich food groups[17, 26] were selected for analysis. These were foods that had high iron content and provide ≥20% of the daily value of iron (18 mg/d)[26, 27] – including red meat, liver meat, beans, nuts, and green leafy vegetables and fish, and foods that enhanced the absorption of non-heme iron from plant-sourced foods – including poultry and fish[28]. Red meat included beef, goat and pork. Dark green leafy vegetables included spinach, lettuce, pumpkin leaves, cowpea leaves, and cassava leaves. Legumes included Bambara nuts, green mung beans, pigeon peas, cow peas, chickpeas, and green peas. Poultry included chicken, nuts included groundnuts, and liver meat included beef liver. The FFQ did not collect information on the intake of fortified breakfast cereals because adults in the study population rarely consumed them. The amount of each food group consumed was estimated by summing the intake of food items in each food group.

Baseline and Follow-up procedures

Clinic visits took place at HAART initiation and monthly until the end of follow-up. At HAART initiation, research nurses administered questionnaires to collect sociodemographic

data and medical history and obtained venous blood samples. The national HIV guidelines do not specify whether and when iron supplementation should be provided, and iron supplementation was neither assessed at baseline nor during follow-up. Participants were followed up until death, loss to follow-up or termination after 24 months of follow-up, or study closure.

Study participants who missed clinic visits were followed up using telephone calls and home visits. The vital status of participants who were not reachable was ascertained by interviewing relatives or neighbors. Research nurses confirmed the clinical condition and treatment of participants that died using standard verbal autopsy techniques [29, 30] and medical record review. Two senior HIV physicians independently reviewed this information and determined a cause of death based on consensus.

Study physicians performed a medical examination at each monthly visit and assessed the HIV disease stage per WHO guidelines [31]. PTB was diagnosed according to Tanzanian National Tuberculosis and Leprosy Programme guidelines [32, 33], and based on one positive sputum sample (of a spot sample, an early morning sputum sample before a second clinic visit, and a third sample at the second clinic visit) following Ziehl-Nielsen staining or chest x-ray with features of tuberculosis in the absence of sputum.

Anthropometry was measured at enrolment and each monthly visit by research nurses using standardized procedures. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters. Weight loss was defined as moderate if 5 – <10%, and severe if ≥10% during follow-up [34]. Incident underweight was defined as BMI <18.5kg/m^2 during follow-up among those with BMI ≥18.5 kg/m^2 at HAART initiation.

Blood samples were collected at enrolment and every 3 – 4 months after that for absolute CD4+ T-cell (FACSCalibur flow cytometer, Becton Dickinson, San Jose, CA) and hemoglobin testing (AcT5 Diff AL analyzer, Beckman Coulter, Miami, FL). Anemia was defined as hemoglobin <120g/L in females and < 130g/L in males, per WHO thresholds for non-pregnant adults[35]. Severe anemia was defined as hemoglobin <80g/L.

Data analysis

Baseline characteristics of included participants were assessed using medians with interquartile ranges (IQR) for continuous variables and percentages for categorical variables. The baseline characteristics of included participants were compared to the characteristics of excluded participants who were alive after 30 days of HAART initiation, had no FFQ completed, had FFQ filled ≥45 d after HAART initiation, or had improbable total energy intake. *P*-values were obtained from the Wilcoxon rank-sum test for continuous variables and the chi-square tests with continuity correction for categorical variables.

Weekly intake of total, animal-sourced, and plant-sourced dietary iron were categorized into quartiles. Quartiles of total dietary iron were ≤66, >66 to 85, >85 to 108, and >108 mg/wk. Quartiles of animal-sourced iron were ≤3, >3 to 5, >5 to 8, and >8 mg/wk. Quartiles of plant-sourced iron were ≤61, >61 to 79, >79 to 100, and >100 mg/wk. The weekly intake of iron-rich food groups was considered in three categories: 0 – 1 servings/wk, 2 –

3 servings/wk, and ≥4 servings/wk. No one in the population had intake of liver meat ≥4 servings/wk, and liver meat was not considered in subsequent analyses.

The outcomes considered for all the analyses were deaths, AIDS-related death, pulmonary TB, severe anemia, underweight, severe and moderate weight loss. AIDS-related death referred to death due to *P jiroveci* pneumonia, pulmonary TB, extrapulmonary TB, Kaposi sarcoma, wasting, opportunistic infection or invasive cervical carcinoma[21, 36]. Severe anemia was defined based on the World Health Organization (WHO) classification as hemoglobin <8g/dl. categories[37]. Underweight was defined based on BMI <18.5 kg/m^2. Individuals with pulmonary TB, severe anemia and underweight at baseline were excluded from the analysis for the respective prospective outcome. Weight loss was estimated based on the difference between the weight measured at each clinic visit and the weight at baseline, as a percentahe of the weight at baseline. Weight loss was regarded as moderate if >5% and severe if >10%.

Using Cox proportional hazards models[38], we estimated the univariable and multivariable-adjusted hazard ratios of prospective clinical outcomes for the categories of intake of dietary iron and iron-rich food groups (compared to the lowest category). The time scale was from FFQ completion to the occurrence of the outcome, administrative censoring, or loss to follow-up.

Baseline variables that have been previously established in the literature to be related to dietary intake and to the main outcome of mortality were included, provided they were unlikely to be along the causal path[39-42]. Multivariable models were adjusted for age (≤30, >30–45, and >45years), sex (male/female), BMI (<18.5, 18.5 – <25, 25 – <30, ≥30kg/m^2), season of FFQ assessment (December–March [dry], April–May [long rains], June–September [harvest], and October–November [short rains]), ownership of household assets (0 – 2, 3 – 6, and 7 – 10), marital status (single/never married, married/cohabiting, divorced/widowed), total energy (quintiles) and clinical trial arm (high dose, standard RDA dose). Baseline hemoglobin and WHO stage was not adjusted for in the main analysis because they could be considered on the causal pathway from dietary iron intake to the outcomes of interest. In sensitivity analysis, the baseline WHO stage was included as a covariate in the models since it could be a confounder instead, and the findings compared. P-values for linear trends were obtained by regressing the median values of each category of the exposure variable.

Only 81% of the population had complete data for all covariates adjusted for in models, and missingness was addressed using the missing indicator approach. P-values were two-sided, and significance was set at < 0.05. Statistical analyses were conducted using the Tableone, mice, and survival packages in RStudio1.0.153[43-45].

Ethics

Ethical approval for the parent trial and for secondary use of the data was obtained from the institutional review boards of the Harvard T. H. Chan School of Public Health, Muhimbili University of Health and Allied Sciences, and the Tanzanian National Institute for Medical Research. Informed consent was obtained from participants at enrolment. All participants

received standard care as per the Tanzania Ministry of Health's National Guidelines for the Management of HIV/AIDS.

Results

Of the 3,418 HIV-infected adults who participated in the parent trial, this analysis was limited to the 2293 participants who had dietary information collected at HAART initiation and who were alive 30 days after HAART initiation (Supplementary Figure 1 and Table 1). Participants were in a male:female ratio of 1:2 (723 males, 1565 females). The median age (IQR) was 37yrs (32, 43). The prevalence of mild, moderate, and severe anemia were 21%, 49%, and 14%, respectively. Underweight (BMI <18.5 kg/m^2) was a common finding at presentation (25%). Most participants were at WHO HIV stage 3 or stage 4 at the time of enrolment (76%) and had CD4 cell counts below 200cells/μL (80%). The median (IQR) time to collect dietary information from HAART initiation among included individuals was 28 (28, 29) days. The median (IQR) duration of follow-up was 21 months (11, 33).

Participants who did not have a suitable FFQ for inclusion in the study (N=895) were slightly less likely to have been enrolled during the harvest months from June to September (11% vs. 15%, *P*-value <0.001), more likely to be at stage 4 clinical disease (16% vs. 12%, *P*-value=0.02), and more likely to die (15% vs. 8%, *P*-value <0.001) during follow-up (Supplementary Table 1).

Supplementary Table 2 lists the range of iron content (mg/100g) of the iron-rich food groups, and the medians (IQR) and categories of intake of iron-rich food groups. Dark green leafy vegetables were the most frequently consumed (Median (IQR): 6.9 (3.9 – 9.8), servings/wk) and poultry was the least commonly consumed (Median (IQR): 0.5 (0 – 1.0), servings/wk). The median (IQR) of red meat intake was 2.9 (1.0 – 3.4), servings/wk. Percentage of iron intake contributed by the food groups was 17% for dark green leafy vegetables, 17% for legumes, 5% for fish, 3% for nuts, and 2% for red meat.

The median (IQR) of weekly intake was 5 mg (3, 8) for animal-sourced iron, 79 mg (61, 100) for plant-sourced iron, and 85 mg (66, 108) for total dietary iron. Individuals who consumed the highest quartile of animal-sourced iron (Table 2) had a lower incidence of all-cause (HR=0.56; 95% CI: 0.35, 0.90) and AIDS-related deaths (HR=0.50; 95%CI: 0.30, 0.90), compared to those who consumed the lowest quartile. The HR for all-cause mortality was 1.85 (95% CI: 0.89, 3.86) among individuals with the highest quartile of plant-sourced iron (Table 3), and 1.85 (95% CI: 0.87, 3.91) among individuals with the highest quartile of total dietary iron (Supplementary Table 3) compared to individuals with their lowest quartile respectively.

Red meat intake was associated with a lower risk of all-cause mortality (HR: 0.54; 95% CI: 0.35 – 0.83), AIDS-related mortality (HR: 0.49; 95% CI: 0.28 – 0.85) and severe anemia (HR: 0.57; 95% CI: 0.35 – 0.91), when intake ≥4 servings/wk, compared to 0 – 1 servings/wk, Table 4 and Supplementary Table 4). The HR for fish intake was 0.40 (95% CI: 0.21 – 0.75) for incident PTB among those with ≥4 servings/wk (vs. 0 – 1 servings/wk, Supplementary Table 5). The HR of all-cause mortality was 0.98 (95% CI: 0.45, 2.18)

among individuals who consumed ≥4 servings/wk of poultry compared to counterparts who consumed 0 – 1 servings/wk. Intake categories of fish and poultry (Supplementary Table 6) were not related to the incidence of the other HIV-related outcomes.

Intake of legumes was associated with 51% (95% CI: 23%, 69%) lower risk of all-cause mortality and 63% (95% CI: 39% – 77%) lower risk of AIDS-related mortality among those with ≥4 servings/wk, compared to 0 – 1 servings/wk (Table 4 and Supplementary Table 7). There were no significant relationships of the intake categories of legumes, dark green vegetables (Supplementary Table 8), and nuts (Supplementary Table 9) with the other outcomes considered.

Discussion

Higher intake of animal-sourced iron among PLWHIV initiating HAART at an urban treatment program in Tanzania was associated with reduced mortality risk, while intake of plant-sourced and total dietary iron was not related to HIV-related outcomes. Intake of iron-rich food groups such as red meat and legumes was associated with a lower risk of mortality and severe anemia.

Dietary iron is an important component of good quality diet[46] and animal-source foods can be important sources of dietary iron. In the absence of sufficient dietary iron, ID results. ID impairs the immune response in PLWHIV by limiting heme oxygenase expression and activity in response to infection[47]. Heme, the by-product of heme oxygenase activity, slows the growth of HIV and *Mycobacteriae* [48]. ID also lowers B cell proliferation and the production of antibodies[49], which mediate cytotoxicity and suppress viremia to slow down HIV disease progression [50, 51]. In our study, intake of animal-sourced iron was associated with a lower risk of both AIDS-related mortality and all-cause mortality, though intake of these food groups was low, and they contributed <10% of the iron content of the diet. Heme iron is likely the key driver of these findings. Animal foods are rich in heme iron, which is well-absorbed and only minimally affected by inhibitors such as calcium, polyphenols, and phytates[17, 52]. In particular, red meat contains the highest amounts of heme iron, and we found similar findings for red meat intake as for overall animal-sourced iron intake. In addition, red meat intake was associated with a reduced risk of severe anemia, underscoring the importance of dietary iron in normal erythropoiesis and immune function.

Our findings with respect to animal-sourced iron may be alternatively attributed to ferritin iron intake, and dietary protein intake as red meat is also a chief source of animal protein[53]. Organ meats such as liver are rich in ferritin iron, a type of non-heme iron that is better absorbed than heme iron[17]. The ferritin protein is a highly efficient store that retains and transports multiple iron atoms together, rather than singly as for heme iron[54]. We were unable to examine the influence of liver iron on HIV-related outcomes due to limited variation in our data, and future studies in settings with greater intake of liver may help clarify its significance. Protein intake is essential to prevent protein-energy malnutrition and sustain the production of antibodies and protein factors important in immunity[55]. Meat protein also enhances the absorption of dietary iron[17]. Thus, intake of iron-rich animal foods may be beneficial among PLWHIV.

There are noteworthy concerns that red meat intake may be unsafe. Red meat intake is associated with increased cardiovascular risk factors[56], higher levels of atherogenic metabolites of gut microbiota[57], as well as increased incidence of and mortality from chronic diseases such as cancers, diabetes, and stroke[58-64] based on studies from high-income countries (HIC). Red meat consumption is much higher in HICs compared to LMICs, on average[65]. While the average red meat intake in North America and Europe varies from 45 – 86 g/d[65], the average red meat intake in our population was 12 g/d, partly due to the high costs of beef and other red meat relative to income and the inconsistent supplies[66, 67]. A recent study among rural Tanzanian Maasai residents in the Ngorongoro Conservation Area who consume a considerable amount of animal-source foods found that red meat intake is associated with hyperlipidemia[68]. However, our finding of a lower risk of all-cause mortality is likely because iron deficiency (ID) was common in our population of PLWHIV. In a randomly selected subcohort of this population, the prevalence of ID and iron deficiency anemia (IDA) were 19% and 15%, respectively[20]. Thus, given the potential harm of excessive red meat intake and the availability of alternatives, public health recommendations to prevent ID based on red meat intake should only target those with relatively small red meat intake. Clinical targets to quickly increase iron stores through diet can be achieved through small increases in intake of red meat and organ meats such as liver, depending on individual and cultural preferences.

Plant-source foods account for the greater component of total dietary iron intake in this setting. In our study, dark green leafy vegetables and legumes together accounted for 34% of total dietary iron intake. Plant-source foods are rich in non-heme iron. Non-heme iron absorption is highly variable depending on the intake of enhancers such as ascorbic acid and animal proteins and inhibitors such as phytates, polyphenols, and calcium[17, 52]. We found no significant association of plant-sourced iron intake with the risk of any of the outcomes considered. While we similarly had null findings with respect to dark green vegetable intake for all outcomes considered, we found greater intake of legumes to be related to a lower risk of all-cause and AIDS-related mortality. Our null findings with respect to dark green vegetables, in particular, are likely because dark green vegetables are rich in phytates, which inhibit iron absorption[69, 70]. Our significant findings regarding legumes are, possibly, because legumes are important sources of iron and protein [71]. Legumes are rich in ferritin iron which is very readily absorbed[12, 54], and its intake likely reduces ID with implications for both erythropoiesis and the immune response. Legumes are also rich in essential amino acids such as lysine. Lysine increases the expression of amino acid transporters in the intestine, improving the digestion of animal and plant-sourced proteins[72], and suppresses proinflammatory cytokine levels, thus modulating intestinal inflammation[72]. Adequate protein intake prevents loss of lean body mass, which is related to wasting, cachexia, and protein-energy malnutrition (PEM [73]). PEM is associated with decreases in T-cell and antigen-specific immune responses[74, 75].

Our study has several noteworthy strengths and limitations. The FFQ used in our study was recently validated[23] and included a detailed list of 119 foods and meals to aid participant recall. We adjusted for several risk factors, including participant characteristics, socioeconomic status, and clinical condition, likely limiting the potential for confounding. Our results were robust to whether the baseline WHO stage was adjusted for or not.

Total energy intake was included in the multivariable models. Therefore, it is unlikely that the relationships we observed were those of the quantity of intake alone rather than the component foods or nutrients. The large sample size of our study made it more likely that our findings were unlikely to be due to random chance alone.

Our study also had a number of limitations. Of the 3,188 participants alive >30 d after HAART initiation, participants who did not have a suitable FFQ and were excluded from the analysis were more likely to be at stage 4 clinical disease at HAART initiation and more likely to have died during follow-up. Nonetheless, the baseline distributions of age, sex, CD4, WHO stage and hemoglobin categories of included participants were consistent with those of the general population of PLWHIV in Dar es Salaam[76]. It is unlikely that intake of animal-sourced iron, red meat, or legumes was harmful enough in the excluded sample to fully explain away the hazard ratios and confidence intervals we obtained. Despite the large sample size, it remains possible that there was insufficient power to examine relationships where the effect may be minimal or outcomes rare.

Our observational study of dietary intake among PLWHIV identified significant relationships of intake or animal-source iron, red meat and legumes with the risk of important HIV-related outcomes including mortality. Implementation science research and public health programs to evaluate approaches to improve the intake of some of these food groups should be considered, as part of good quality diets. These can include voucher incentives for groceries, cooking classes, nutritional counseling during clinic visits, and reminders via video and text message format, appropriate to the peculiarities of each population[77, 78]. Some of these incentives also strengthen linkages to and retention in care among PLWHIV [79, 80], and would likely improve intake of good quality diet as well. Intake of red meat, for instance, is very low in many African communities, but, as highlighted in our studies, small increases in intake are likely to meaningfully improve health outcomes among PLWHIV. Policy-makers and stakeholders should prioritize nutritional education and support in HIV care.

Conclusion

We examined the relationships of intake of dietary iron and iron-rich food groups with all-cause mortality and HIV-related outcomes. We found that intake of animal-sourced iron, red meat, and legumes was associated with lower mortality risk. Public health guidelines to promote effective iron intake may recommend greater consumption of legumes, and targeted increases in consumption of red meat, in settings where ID is highly prevalent. Policy-makers and stakeholders should prioritize nutritional education and support in HIV care. Additional research would help further elucidate the mechanisms behind these findings and determine the best approaches to promote better dietary intake among PLWHIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

AIA, MH, CRS,and WF designed the research. RAN, SI, ZL, FM, and WF conducted the research. AIA, CRS, MH and WF analyzed the data and wrote the paper. WF has primary responsibility for the final content. All authors contributed to drafting the manuscript, reviewed and approved the final version.

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Abbreviations used in the text:

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
BMI	Body Mass Index
CBC	Complete blood count
CI	Confidence Interval
HAART	Highly Active Antiretroviral Therapy
HR	Hazard ratio
ID	iron deficiency
IDA	Iron deficiency anemia
IQR	Interquartile range
LMIC	Low and Middle Income Countries
NTBI	Non-transferrin bound iron
PLWHIV	People living with HIV
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error
TB	Tuberculosis

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Table 1.

Clinical and sociodemographic characteristics among patients initiating HAART in Dar es Salaam, Tanzania, 2006-2008 (N=2293)

Characteristics	Categories	N (%)†
Age (yrs)	Median (±IQR)	37 (32, 43)
	<30	343 (15%)
	30-<45	1491 (65%)
	≥45	457 (20%)
Sex	Female	1565 (68%)
	Male	723 (32%)
Body mass index, kg/m2	Median (±IQR)	20.6 (18.5, 23.3)
	<18.5	572 (25%)
	18.5 to <25	1357 (60%)
	25 to <30	270 (12%)
	≥30	82 (4%)
Household assets‡	0-3	816 (39%)
	4-7	949 (46%)
	8-9	305 (15%)
Hemoglobin, mg/dl	Median (±IQR)	102 (88, 117)
	No anemia	350 (16%)
	Mild anemia	450 (21%)
	Moderate	1066 (49%)
	Severe anemia	314 (14%)
CD4 cell count, cells/μL	Median (±IQR)	125 (59, 190)
	<200	1757 (80%)
	200 – <350	421 (19%)
	≥350	33 (2%)
WHO HIV Clinical stage§	1	123 (6%)
	2	390 (18%)
	3	1362 (64%)
	4	255 (12%)
History of tuberculosis	No	1602 (77%)
	Yes	488 (23%)
District	Ilala	903 (42%)
	Kinondoni	634 (30%)
	Temeke	584 (28%)
Multivitamin	Standard RDA	1132 (49%)
	High-dose	1161 (51%)
Season	Dry (Dec–Mar)	269 (12%)
	Long rains (Apr–May)	1024 (45%)
	Harvest (Jun–Sep)	347 (15%)
	Short rains (Oct – Nov)	653 (29%)

[†]Values in the column are number (column percent), or median (IQR) among the exposed. Column percents may not add to 100 due to rounding.

[‡]Household assets were computed from a list of assets that included a sofa, television, radio, refrigerator, fan, electricity, potable water, bike and car

[§]Abbreviations: WHO: World Health Organization

Table 2.

Association of dietary intake of animal-sourced iron and prospective clinical outcomes among Tanzanian adults initiating HAART in Dar es Salaam, Tanzania, 2006 – 2008 (N=2293)

	Categories of animal-sourced iron intake											
	1st Quartile, N=583		2nd Quartile, N=602			3rd Quartile, N=356			4th Quartile, N=752			*P*-value[§]
Incident clinical outcomes	**n/N, %[†]**	**Ref HR (95% CI)**	**n/N, %[†]**	**Univariable HR (95% CI) [‡]**	**Adjusted HR (95% CI) [‡]**	**n/N, %[†]**	**Univariable HR (95% CI) [‡]**	**Adjusted HR (95% CI) [‡]**	**n/N, %[†]**	**Univariable HR (95% CI) [‡]**	**Adjusted HR (95% CI) [‡]**	**Linear trend[§]**
Deaths, N=2293	59/583, 10%	Ref	45/602, 8%	0.74 (0.50, 1.09)	0.72 (0.48, 1.08)	22/356, 6%	0.61 (0.37, 0.99)	0.54 (0.32, 0.92)	49/752, 7%	0.64 (0.44, 0.94)	0.56 (0.35, 0.90)	0.01
AIDS-related death, N=2293	39/583, 7%	Ref	32/602, 5%	0.80 (0.50, 1.27)	0.76 (0.47, 1.224)	15/356, 4%	0.62 (0.34, 1.13)	0.57 (0.30, 1.08)	30/742, 4%	0.60 (0.37, 0.96)	0.50 (0.30, 0.90)	0.02
Pulmonary TB , N=2145	25/547, 5%	Ref	18/556, 3%	0.75 (0.41, 1.37)	0.68 (0.37, 1.28)	6/327, 2%	0.42 (0.17, 1.02)	0.36 (0.14, 0.92)	244/715, 3%	0.76 (0.43, 1.33)	0.61 (0.32, 1.16)	0.11
Severe anemia, N=1684	40/404, 10%	Ref	43/462, 9%	1.03 (0.67, 1.59)	0.97 (0.62, 1.53)	22/264, 8%	0.88 (0.52, 1.48)	0.78 (0.45, 1.36)	43/554, 8%	0.80 (0.52, 1.23)	0.73 (0.45, 1.21)	0.16
BMI <18.5, N=1837	48/426, 11%	Ref	54/498, 11%	1.07 (0.72, 1.58)	1.05 (0.71, 1.57)	27/289, 9%	0.86 (0.54, 1.38)	0.82 (0.50, 1.35)	48/624, 8%	0.72 (0.48, 1.08)	0.69 (0.44, 1.09)	0.07
Severe weight loss, ≥10%, N=2242	76/568, 13%	Ref	58/586, 10%	0.79 (0.56, 1.12)	0.76 (0.53, 1.07)	44/351, 13%	1.05 (0.72, 1.52)	0.95 (0.64, 1.41)	71/737, 10%	0.78 (0.56, 1.07)	0.68 (0.47, 0.99)	0.09
Moderate weight loss, ≥5%, N=2242	138/568, 24%	Ref	106/86, 18%	0.78 (0.60, 1.00)	0.78 (0.60, 1.01)	71/351, 20%	0.89 (0.67, 1.18)	0.87 (0.65, 1.19)	146/737, 20%	0.86 (0.69, 1.09)	0.86 (0.66, 1.13)	0.43

[†] *N* represents participants included in the category, while *n* is the number of individuals who experienced an event. Individuals with the clinical condition or outcome at baseline were excluded. The proportion of participants with the outcome in each category of the exposure was %. Food items considered as animal-sourced included red meat (beef, goat and pork), poultry, fish, liver, eggs and dairy.

[‡] Hazard ratios (HR) and confidence intervals were estimated from Cox proportional hazards regression. HR above 1 implies that the incidence of the outcome was greater among participants with the exposure, compared to those without the exposure. HR below 1 implies that the incidence of the outcome was less among participants with the exposure, compared to those without the exposure.

Multivariable estimates adjusted for age (<30, 30 – 50 and >50 years), sex (female, male), body mass index (less than 18.5, 18.5 to 24.99, above 25 kg/m2), season of FFQ assessment (December–March [long rains], April–May [harvest], June–September[postharvest], and October–November [short rain]), ownership of household assets (0 – 2, 3 – 6 and 7 - 10), marital status (single/never married, married/cohabiting, divorced/widowed), total energy (quintiles) and clinical trial arm. In addition, interaction terms for the clinical trial arm with each of season and marital status were included in the model.

[§] P-values for linear trend were obtained from Cox proportional hazards model using the median values of each category of the exposure variable.

Table 3.

Association of dietary intake of plant-sourced iron and prospective clinical outcomes among Tanzanian adults initiating HAART in Dar es Salaam, Tanzania, 2006 – 2008 (N=2293)

	Categories of plant-sourced iron intake											
	1st Quartile, N=586		2nd Quartile, N=568			3rd Quartile, N=526			4th Quartile, N=612			*P*-value
Incident clinical outcomes	**n/N, %†**	**Ref HR (95% CI)**	**n/N, %†**	**Univariable HR (95% CI) ‡**	**Adjusted HR (95% CI) ‡**	**n/N, %†**	**Univariable HR (95% CI) ‡**	**Adjusted HR (95% CI) ‡**	**n/N, %†**	**Univariable HR (95% CI) ‡**	**Adjusted HR (95% CI) ‡**	**Linear trend§**
Deaths, N=2293	46/586, 8%	Ref	42/568, 7%	0.93 (0.62, 1.42)	1.48 (0.89, 2.46)	38/526, 7%	0.94 (0.61, 1.44)	1.40 (0.73, 2.70)	49/613, 8%	1.03 (0.69, 1.54)	1.85 (0.89, 3.86)	0.12
AIDS-related death, N=2293	32/586, 6%	Ref	27/568, 5%	0.86 (0.52, 1.44)	1.50 (0.81, 2.76)	23/526, 4%	0.81 (0.48, 1.39)	1.56 (0.71, 3.42)	34/613, 6%	1.03 (0.63, 1.66)	1.96 (0.81, 4.76)	0.15
Pulmonary TB , N=2145	14/549, 3%	Ref	16/533, 3%	1.21 (0.59, 2.48)	0.87 (0.37, 2.01)	22/497, 4%	1.91 (0.98, 3.74)	1.29 (0.51, 3.30)	21/566, 4%	1.52 (0.77, 3.00)	1.20 (0.42, 3.39)	0.56
Severe anemia, N=1684	32/418, 8%	Ref	36/424, 9%	1.17 (0.73, 1.89)	1.23 (0.71, 2.14)	39/401, 10%	1.35 (0.85, 2.16)	1.46 (0.76, 2.80)	41/441, 9%	1.25 (0.79, 1.99)	1.82 (0.88, 3.75)	0.10
BMI <18.5, N=1837	46/463, 10%	Ref	47/459, 10%	1.08 (0.72, 1.63)	0.99 (0.62, 1.60)	40/430, 9%	1.04 (0.68, 1.59)	0.91 (0.50, 1.65)	44/485, 9%	0.93 (0.62, 1.41)	0.79 (0.40, 1.54)	0.55
Severe weight loss, ≥10%, N=2242	73/574, 13%	Ref	63/553, 11%	0.93 (0.66, 1.30)	0.90 (0.60, 1.35)	44/518, 9%	0.74 (0.51, 1.08)	0.71 (0.43, 1.19)	69/597, 12%	0.95 (0.68, 1.32)	1.00 (0.57, 1.76)	0.85
Moderate weight loss, ≥5%, N=2242	135/574, 24%	Ref	118/553, 21%	0.92 (0.72, 1.18)	1.03 (0.77, 1.38)	90/518, 17%	0.79 (0.61, 1.04)	0.92 (0.63, 1.34)	118/597, 20%	0.86 (0.67, 1.10)	1.03 (0.67, 1.58)	0.99

† *N* represents participants included in the category, while *n* is the number of individuals who experienced an event. Individuals with the clinical condition or outcome at baseline were excluded. The proportion of participants with the outcome in each category of the exposure was %.

‡ Hazard ratios (HR) and confidence intervals were estimated from Cox proportional hazards regression. HR above 1 implies that the incidence of the outcome was greater among participants with the exposure, compared to those without the exposure. HR below 1 implies that the incidence of the outcome was less among participants with the exposure, compared to those without the exposure.

Multivariable estimates adjusted for age (<30, 30 – 50 and >50 years), sex (female, male), body mass index (less than 18.5, 18.5 to 24.99, above 25 kg/m2), season of FFQ assessment (December–March [long rains], April–May [harvest], June–September[postharvest], and October–November [short rain]), ownership of household assets (0 – 2, 3 – 6 and 7 - 10), marital status (single/never married, married/cohabiting, divorced/widowed), total energy (quintiles) and clinical trial arm. In addition, interaction terms for the clinical trial arm with each of season and marital status were included in the model.

§ P-values for linear trend were obtained from Cox proportional hazards model using the median values of each category of the exposure variable.

Occupation - business/professional, skilled formal, skilled informal, unskilled, or unemployed

Table 4.

Intake of iron-rich food groups[†] and all-cause mortality risk among Tanzanian adults initiating HAART in Dar es Salaam, Tanzania, 2006 – 2008 (N=2293)

	Categories								
	0 – 1 servings/wk		2 – 3 servings/wk			≥4 servings/wk			*P*-value
Clinical Outcome	**n/N, %[‡]**	**HR (95% CI)**	**n/N, %**	**Univariable HR (95% CI) [§]**	**Multivariable HR (95% CI) [§]**	**n/N, %**	**Univariable HR (95% CI) [§]**	**Multivariable HR (95% CI) [§]**	**Linear trend[¶]**
Red meat	92/957, 10%	Ref	51/752, 7%	0.72 (0.51, 1.01)	0.66 (0.46, 0.94)	32/584, 6%	0.57 (0.38, 0.85)	**0.54 (0.35, 0.83)**	**0.003**
Dark green vegetables	16/197, 8%	Ref	18/304, 6%	0.74 (0.38, 1.45)	0.77 (0.39, 1.53)	141/1792, 8%	0.98 (0.58, 1.64)	1.14 (0.67, 1.95)	0.32
Legumes	26/187, 14%	Ref	26/305, 9%	0.60 (0.35, 1.02)	0.67 (0.38, 1.17)	77/1801, 4%	0.47 (0.31, 0.72)	**0.49 (0.31, 0.77)**	**0.002**
Poultry	151/1930, 8%	Ref	17/284, 6%	0.78 (0.47, 1.29)	0.90 (0.54, 1.51)	7/79, 9%	1.12 (0.53, 2.40)	0.98 (0.45, 2.18)	0.80
Fish	23/245, 9%	Ref	31/420, 7%	0.79 (0.46, 1.36)	0.73 (0.42, 1.26)	121/1628, 7%	0.80 (0.52, 1.26)	0.88 (0.55, 1.41)	0.91
Nuts	130/1536, 9%	Ref	25/434, 6%	0.69 (0.45, 1.06)	0.69 (0.44, 1.08)	20/323, 6%	0.73 (0.45, 1.16)	0.83 (0.50, 1.37)	0.21

[†] Iron content for each food group varies by the specific food item, and how it is prepared for consumption. Food groups selected based on published review paper by the BRINDA group. Intake of liver was small and did not vary in the population. No one in the population consumed at least 2 servings/wk.

[‡] *N* represents participants included in the category, while *n* is the number of individuals who experienced an event. Individuals with the clinical condition or outcome at baseline were excluded. The proportion of participants with the outcome in each category of the exposure was %.

[§] Hazard ratios (HR) and confidence intervals were estimated from Cox proportional hazards regression. HR above 1 implies that the incidence of the outcome was greater among participants with the exposure, compared to those without the exposure. HR below 1 implies that the incidence of the outcome was less among participants with the exposure, compared to those without the exposure.

Multivariable estimates adjusted for age (<30, 30 – 50 and >50 years), sex (female, male), body mass index (less than 18.5, 18.5 to 24.99, above 25 kg/m2), season of FFQ assessment (December–March [long rains], April–May [harvest], June–September[postharvest], and October–November [short rain]), ownership of household assets (0 – 2, 3 – 6 and 7 - 10), marital status (single/never married, married/cohabiting, divorced/widowed), total energy (quintiles) and clinical trial arm. In addition, interaction terms for the clinical trial arm with each of season and marital status were included in the model.

[¶] P-values for linear trend were obtained from Cox proportional hazards model using the median values of each category of the exposure variable.