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Christopher R. SUDFELD[1*], Ashley BUCHANAN[2], Nzovu ULENGA[3,4], Donna SPIEGELMAN[1,5,6,7], Expeditho MTISI[3], Ellen HERTZMARK[1], Aisa N. MUYA[3], David SANDO[1], Ester MUNGURE[1], Mucho MIZINDUKO[1,8], Wafaie W. FAWZI[1,6,7]

Affiliations:
[1] Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA
[2] Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Kingston, USA
[3] Management and Development for Health, Dar es Salaam, Tanzania.
[4] Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, USA
[5] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, USA
[6] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA
[7] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, USA
[8] Department of Epidemiology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania.

* Corresponding Author

Address for correspondence and reprints:
Author: Christopher R Sudfeld
Email: csudfeld@hsph.harvard.edu
Address: Harvard T.H. Chan School of Public Health Building I, 12th floor, 665 Huntington Avenue Boston, MA 02115
Phone: +001 617 432 5051

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Abstract

Objective: The objective of this study was to assess the effectiveness of a routine multivitamin supplementation program for adults living with HIV in Tanzania.

Design: We conducted a retrospective cohort study of 67,707 adults enrolled in the Dar es Salaam HIV care and treatment program during 2004-2012.

Methods: The Dar es Salaam HIV care and treatment program intended to provide all adult patients with multivitamin supplements (vitamins B-complex, C, and E) free of charge; however, intermittent stockouts and other implementation issues did not afford universal coverage. We use Cox proportional hazard models to assess the time-varying association of multivitamin supplementation with mortality and clinical outcomes.

Results: The study cohort contributed 41,540 and 129,315 person-years of follow-up time to the ART-naïve and ART-experienced analyses, respectively. Among 48,207 ART-naïve adults, provision of multivitamins reduced the risk of mortality (adjusted hazard ratio (aHR): 0.69; 95% CI: 0.59-0.81), incident tuberculosis (TB) (aHR: 0.83; 0.76-0.91), and meeting ART eligibility criteria (aHR: 0.78; 95% CI: 0.73-0.83) after adjustment for time-varying confounding. Among 46,977 ART-experienced patients, multivitamins reduced mortality (HR: 0.86; 95% CI: 0.80-0.92), incident TB (aHR: 0.78; 95% CI: 0.73-0.84), and immunologic failure (aHR: 0.70; 95% CI: 0.67-0.73). The survival benefits associated with provision multivitamins appeared to be greatest during the first year of ART and declined over time (p-value <0.001).

Conclusion: Multivitamin supplementation appears to be a simple, effective, safe, and scalable program to improve survival, reduce incidence of TB, and improve treatment outcomes for adult HIV patients in Tanzania.

Introduction

In 2016 an estimated 19.5 million people accessed antiretroviral therapy (ART), which is the first time that more than half of all people living with human immunodeficiency virus (HIV) were on treatment [1]. Notwithstanding marked success in increasing ART coverage, HIV-infected adults in resource-limited settings still experience high rates of mortality and HIV progression as compared with people living with HIV in high-income settings [2, 3]. Late initiation of ART with low CD4 T-cell counts and comorbidities, concurrent malnutrition, and high risk of exposure to life-threatening pathogens are likely contributors to poor HIV treatment outcomes in resource-limited settings [3, 4]. As a result, interventions to slow CD4 T-cell decline for ART-naïve individuals, improve CD4 T-cell reconstitution after ART initiation, and promote strong, well-balanced immune responses may reduce mortality and improve HIV care and treatment outcomes.

Micronutrient deficiencies are common among HIV-infected adults in sub-Saharan Africa and are known to impact immune responses [5, 6]. Randomized trials among ART-naïve populations have found that multivitamin supplements reduce mortality, disease progression, CD4 T-cell decline, and viral load [7-10]. A recent randomized trial conducted in Botswana determined pre-ART multivitamins containing vitamins B, C, E, and selenium approximately halved the risk of HIV progression or CD4 T-cell decline below the ART initiation threshold of 250 cells/μL [11]. Evidence on the effect of multivitamins for adults on ART is much more limited. Small placebo-controlled trials of ART-adjunct multivitamins have yielded mixed results on CD4 T-cell reconstitution and immunological markers but were underpowered to assess mortality and clinical outcomes [12-15]. A randomized dosing trial of ART-adjunct multivitamin supplements containing multiple recommended daily allowances (RDAs) of

vitamins B-complex, C and E, versus single RDA supplements conducted in Tanzania found no difference in HIV progression; however, it is not clear if single RDA multivitamins provided any benefit due to the lack of a placebo group [16]. To the best of our knowledge, no studies have evaluated the effectiveness of routine pre-ART or ART-adjunct multivitamin supplementation in a programmatic setting.

During 2004 to 2012, the urban Dar es Salaam, Tanzania HIV care and treatment program provided multivitamins containing B-complex, C, and E as standard of care for ART-naive and ART-experienced adult patients. Nevertheless, not all patients received multivitamins due to intermittent stockouts and other implementation issues. In this large observational cohort study, we examined the association of multivitamin supplement provision with mortality and treatment outcomes for ART-naïve and ART-experienced adult patients.

Methods

Study Population

This study was a retrospective cohort of HIV-infected adult (≥ 15 years of age) men and non-pregnant women who were enrolled in the Management and Development for Health (MDH)-supported HIV care and treatment program in Dar es Salaam, Tanzania from November 2004 to September 2012. The study cohort was additionally restricted to individuals who attended at least two clinic visits to ensure adequate follow-up for ascertainment of health outcomes. Patients could contribute to both ART-naive and ART-experienced periods. The MDH HIV care and treatment program was established in 2004 as a partnership between Muhimbili University of Health and Allied Sciences, Dar es Salaam City Council, and Harvard University with financial support from the Center for Disease Control's Presidents' Emergency

Plan for AIDS Relief (PEPFAR). During the study period, the MDH program provided HIV care and treatment at 47 HIV clinic sites in Dar es Salaam.

Patient Enrollment, Follow-up, and Standard of Care

All HIV-infected adults enrolled in the program received clinical care and treatment following Tanzanian national and World Health Organization (WHO) guidelines [17, 18]. ART-naïve adult patients were scheduled for clinic visits every 3 to 6 months to receive a clinical exam and re-assess for ART eligibility. During 2004 to 2012, all adult patients with WHO HIV stage IV disease, CD4 cell count less than 200 cells/μL, or WHO HIV stage III disease with a CD4 T-cell count less than 350 cells/μL were considered eligible for ART initiation [19]. The multivitamin supplementation program ended in 2012 primarily for financial reasons. The Dar es Salaam HIV care and treatment program instituted a Test-and-Treat strategy in 2016, which occurred after the end of the multivitamin program and beyond the range of data included in this study. Antiretroviral drugs were provided free of charge by the Tanzanian government and standard first-line regimens included two nucleoside reverse-transcriptase inhibitors (NRTIs) [lamivudine (3TC) or emtricitabine (FTC), as well as stavudine (d4T) or zidovudine (ZDV) or Tenofovir (TDF)], and one non-nucleoside reverse-transcriptase inhibitor (NNRTI) [efavirenz (EFV) or nevirapine (NVP)]. Cotrimoxazole prophylaxis was recommended when CD4 T-cell counts were less than 200 cells/μL, and treatment protocols for all opportunistic infections followed WHO guidelines [17, 18].

Adults receiving ART were scheduled for clinic visits at 2 weeks post-initiation and monthly thereafter. Physicians and nurses completed standardized patient forms at each visit to capture demographic and clinical information. Patients were screened for tuberculosis (TB)

based on a TB screener consisting of cough, fever, night sweats, weight loss and hemoptysis. Sputum smears and chest radiographs were administered to those suspected to have TB to assist with diagnosis. Nurses measured height at the initial clinic visit and weight and middle upper arm circumference at subsequent clinic visits. Body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the height in meters squared (kg/m^2). Laboratory assessments of CD4 T-cell count, hemoglobin (Hb), and alanine aminotransferase (ALT) concentrations were scheduled to be performed at program enrollment, time of ART initiation and every 6 months during follow-up. HIV viral load quantification was not available during the study period.

Provision and composition of multivitamin supplements

The Dar es Salaam HIV program decided to provide all ART-naïve and ART-experienced adult patients multivitamins free of charge as standard of care based on findings from a randomized trial of multivitamins conducted among Tanzanian HIV-infected pregnant women in the pre-ART era and from other multivitamin studies [7-9, 15, 16, 20]. During the study period, intermittent stockouts and other implementation issues (e.g., physician decision or error, missing pharmacy pickup, patient refusal, etc.) occurred which resulted in less than universal coverage. Adult ART-naïve participants received high-dose multivitamin supplements as standard of care that contained 2 to 21 times the RDA of B vitamins (20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B6, 100 mg niacin, 50 µg vitamin B12, 0.8 mg folic acid), 2 times the RDA for vitamin E (30 mg), and 6 times the RDA for vitamin C (500 mg). Adults on ART received multivitamin supplements that contained a single RDA of B vitamins (1.2 mg thiamin, 1.2 mg riboflavin, 1.2 mg vitamin B6, 15 mg niacin, 2.4 µg vitamin B12, 0.4 mg folic acid),

vitamin E (15 mg), and vitamin C (80 mg). Single RDA multivitamins were provided for patients on ART since a randomized trial among Tanzanians on ART determined that multiple RDA multivitamins increased ALT to levels that suggest liver toxicity [16]. Between 2004 to 2010 the multivitamin supplements used in the program were produced by Tishcon Corporation (Salisbury, MD, USA) and by Elys Chemical Industries (Nairobi, Kenya) from 2010 to 2012.

Statistical Analysis

All analyses were stratified by ART-naïve and ART-experienced follow-up periods due to differences in multivitamin dosage and due to the potential for effect modification by concurrent use of ART. The status of time-varying multivitamin provision was updated at each patient's visit. The outcomes of interest for ART-naïve and ART-experienced patients included incident events of all-cause mortality, anemia (men Hb <13 g/dL; women Hb <12 g/dL), severe anemia (Hb <8.5 g/dL for both sexes), wasting (BMI <18.5 kg/m2), TB, WHO stage III or IV disease, any increase in WHO stage, and elevated liver enzymes (ALT >40 IU/L and ALT >200 IU/L). ART eligibility defined by WHO stage and CD4 T-cell criteria was also included as an outcome for the ART-naïve period. Among ART-experienced adults, immunologic failure was defined as meeting at least one of the following on or after 168 days on ART: a CD4 less than or equal to CD4 at the time of ART initiation, CD4 less than half of the maximum value, or CD4 less than 100 cells/µl [21, 22].

The Andersen-Gill formulation of the Cox proportional hazard model was used to evaluate the time-varying effect of multivitamin provision at the prior visit on subsequent outcomes of interest [23]. During the ART-naïve period, time was measured as the interval since MDH enrollment, and during the ART-experienced period, the interval since ART initiation. For both groups, follow-up began at the time of their first multivitamin ascertainment. Patients were

censored at the date of death (for non-mortality outcomes), loss to follow-up (last clinic visit), or the last clinic visit date of this study (September 30, 2012). In the ART-naïve analyses, patients were also censored at the time of ART initiation. Covariates that were associated with mortality at a p-value less than 0.20 in the univariate analysis were included in the adjusted models. The covariates considered for confounding adjustment included: age at visit, sex (male, female), district (Ilala, Kinondoni, Temeke), facility level (hospital, health center, dispensary), height (cm), BMI, MUAC (<20, 20 to <22, 22 to <25, 25 to <27, ≥27 cm), CD4 T-cell count , hemoglobin concentration, ALT, tuberculosis (yes, no), WHO HIV stage (I, II, III, IV), and on ART at enrollment (yes, no for ART period). The possible nonlinear relationship between continuous covariates (age, height, BMI, CD4 T-cell count, hemoglobin concentration, and ALT) with study outcomes was examined with restricted cubic splines [24, 25]. In sensitivity analyses, we evaluated potential effect modification of the association of multivitamins with outcomes by time. We used cross-product terms which multiplied time-varying multivitamin use by time since first multivitamin assessment as a continuous variable and compared models with and without this term, with a one degree of freedom likelihood ratio test to assess statistical significance of effect modification by time. In addition, we assessed potential bias due to dependent censoring (i.e., loss to follow-up) using inverse probability of censoring weights [26]. Because no bias was evident in the mortality analysis, we did not pursue this sensitivity analysis further for the other outcomes. All statistical tests were two-sided at a 0.05 significance level, and conducted using SAS 9.3 (Cary, North Carolina, USA).

Ethics

The institutional review boards at the Harvard T. H. Chan School of Public Health (20032) and the Tanzanian National Institute of Medical Research (NIMR/HQ/R.8a/Vol IX/1668) approved the study. The study conformed to the principles embodied in the Declaration of Helsinki.

Results

The study cohort consisted of 67,707 HIV-infected non-pregnant adult patients who attended 1,731,385 clinic visits and were followed for 170,855 person-years between 2004 to 2012. A total of 48,207 adults contributed to the ART-naïve analysis with 288,934 patient-visits (median 3 visits per patient) and 41,540 person-years of follow-up. As for the ART-experienced analysis, 46,977 patients contributed data from 1,389,218 patient-visits (median 25 visits per patient) with 129,315 person-years of follow-up time. Characteristics of ART-naïve and ART-experienced patients at their first multivitamin ascertainment (baseline) are presented in Table 1. The mean ages at baseline were 36.4 (standard deviation (SD): 9.7) and 37.7 years (SD: 9.6) for ART-naïve and ART-experienced patients, respectively. At the first multivitamin ascertainment during the ART-experienced period, the mean CD4 T-cell count was 192 cells/µl (SD: 173), and 79% of patients had WHO stage III or IV disease. In addition, 77% and 80% of ART-naïve and ART-experienced patients were anemic, respectively.

Multivitamin supplementation among ART-naïve patients

Multivitamins were provided to 86% of patients at the baseline ART-naïve clinic visit. As a sign of minimal potential for confounding by indication, adult ART-naïve patients who received multivitamins at the baseline visit were similar, on average, to those who did not

receive multivitamins in terms of age, sex, BMI, CD4 T-cell count, anemia status, TB co-infection, and WHO HIV stage (Supplementary Table 1).

The unadjusted and time-varying covariate adjusted hazard ratios for the relationship of multivitamin provision with mortality and HIV progression among ART-naïve adults are presented in Table 2. Multivitamin provision was associated with reduced risk of all-cause mortality in univariate (hazard ratio (HR): 0.54; 95% CI: 0.47-0.62) and time-varying adjusted (aHR: 0.69; 0.59-0.81) analyses. Provision of multivitamins was also associated with reduced risk of reaching ART eligibility criteria and incident anemia, wasting, tuberculosis and WHO stage III or IV disease in time-varying adjusted models. Multivitamin provision also reduced the risk of incident ALT >40 in time-varying adjusted models. In sensitivity analyses evaluating effect modification by time, we found that the protective association of multivitamins with incident severe anemia, wasting, WHO Stage III or IV disease, and ALT > 40 IU/L became stronger over time (p-values for effect modification by time<0.05) (Supplementary Table 3).

Multivitamin supplementation among ART-experienced patients

Among HIV-infected adults receiving ART, multivitamins were provided at 59% of the baseline clinic visits. ART-experienced patients who received multivitamins at the baseline visit were similar, on average, to those who did not receive multivitamins in terms of age, sex, BMI, CD4 T-cell count, anemia status and WHO HIV stage suggesting minimal confounding by indication (Supplementary Table 2).

The unadjusted and time-varying adjusted hazard ratios for the relationship of multivitamin use with health outcomes among ART-experienced patients are presented in Table 3. Multivitamin provision was associated with decreased risk of mortality (HR: 0.86; 95% CI: 0.80- 0.92) and immunologic failure (HR: 0.70; 0.67- 0.73) in time-varying adjusted models.

ART-adjunct multivitamins also reduced the risk of incident anemia, severe anemia, wasting, tuberculosis, and ALT >40 IU/L at subsequent clinic visits. There was no association of multivitamin provision with incident WHO HIV stage III or IV disease or increase in WHO HIV stage among adults on ART. In sensitivity analyses, the magnitude of the protective association of multivitamins with incident anemia, wasting, and immunologic failure became stronger over time (p-values for effect modification by time<0.05; Supplementary Table 4). In contrast, the protective association of multivitamins on mortality attenuated over time (p-value for effect modification by time<0.05; Supplementary Table 4) and there was some indication of a harmful association after 3 years of ART (aHR: 1.22; 95% CI: 1.06- 1.41). The results indicating effect modification of the mortality association by time were materially unchanged when we adjusted for dependent censoring using inverse probability of censoring weights (results not shown). However, after adjusting for dependent censoring, the harmful association after 3 years on ART was elevated but no longer statistically significant (aHR: 1.20; 95% CI: 0.98-1.46).

Discussion

In this large implementation evaluation of a multivitamin supplementation program for HIV-infected adults enrolled in the Dar es Salaam HIV care and treatment program, we found that routine provision of multivitamin supplements containing vitamins B-complex, C, and E provided benefits for both ART-naïve and ART-experienced patients. Among ART-naïve patients, multivitamin supplements reduced the risks of mortality, reaching ART eligibility criteria and incident anemia, TB, and WHO HIV disease stage progression. Similarly, among ART-experienced patients, multivitamins reduced the risks of mortality, immunologic failure, and incident TB, anemia, and wasting. It is important to note that the mortality benefits for

patients on ART appeared to be greatest, and possibly limited to, the first year of antiretroviral treatment. Multivitamins were also found to be safe in terms of hepatotoxicity as assessed by ALT for both ART-naïve and ART-experienced patients.

Our finding that programmatic provision of multivitamins reduces mortality and improves care outcomes for ART-naive patients aligns with the findings of multiple randomized placebo-controlled trials [7-11]. Most countries and programs in sub-Saharan Africa have shifted to a 'Test-and-Treat' strategy for ART initiation, including Tanzania in 2016. Nevertheless, our results indicate that the benefits of multivitamin supplementation for ART-naïve determined in randomized trials were replicated at scale, which lends support for a potential effect among patients on ART. The mechanisms by which vitamins B-complex, C, and E improve outcomes for HIV-infected adults are not completely understood, but it is postulated antioxidant, immunomodulatory, and viral replication inhibitive properties are primary contributors [6, 11]. The B vitamins are important for lymphocyte proliferation, natural killer cell cytotoxicity, and cell-mediated immunity [27]; vitamin C supplementation can improve lymphocyte proliferation [28]; and vitamin E may inhibit HIV replication [29]. A randomized trial conducted in Botswana also indicated that the addition of selenium to multivitamins containing vitamins B, C, E may provide even greater CD4 T-cell and HIV progression benefits for ART-naïve patients [11]. Selenium is immunostimulatory and has notable antioxidant and antiviral properties which may influence HIV replication [30]. As a result, although we found multivitamins containing vitamins B, C, and E improved treatment outcomes for ART-naïve adults, the addition of selenium as well as other micronutrients and minerals may provide additional benefit. Studies and randomized trials are warranted to determine the optimal composition and dosage of multivitamin supplements for HIV-infected adults.

Program provision of multivitamins also improved survival and reduced the incidence of anemia, immunologic failure, wasting and TB for HIV-infected adults receiving ART; however, the magnitude of benefit appeared to be attenuated as compared to ART-naïve patients. It is conceivable that the relative contribution of multivitamins to survival and improved health outcomes may be comparatively less in the presence of the strong beneficial effects of ART. In addition, sensitivity analyses examining effect modification by time revealed that the survival benefits associated with multivitamins might be limited to the first year of ART. Multivitamins may provide greater beneficial effects on inflammation, immune reconstitution inflammatory syndrome (IRIS) and HIV-related causes of death which occur more frequently during the initial year of ART [31]. Our analysis also indicated a potentially harmful effect on mortality for ART-experienced patients who were on ART for 3 years or more, while at the same time we found that multivitamins decreased the risk of anemia, wasting, and immunologic failure for these patients. We are unable to explain the biological mechanisms leading to these somewhat contradicting findings but cannot rule out residual confounding by indication. Overall, programs that provide multivitamins only during the first year of ART when risk of mortality is greatest may be more beneficial in terms of survival impact and cost-effectiveness. Impact evaluations of multivitamin program in others settings are warranted.

In contrast to the consistent evidence base for ART-naïve patients, randomized trials of multivitamins for ART-experienced patients have determined mixed results on CD4 T-cell reconstitution and other immunological markers [12-16]. A randomized trial conducted among 40 HIV-infected adults on ART in the US found multivitamin and mineral supplements improved CD4 T-cell counts after 3 months as compared with placebo [13]. In contrast, a recent trial of 400 HIV-infected Ugandan adults initiating ART found no effect of single RDA

supplements containing vitamins B, C, and E on CD4 T-cell counts up to 18 months [12]. Nevertheless, these trials had very limited statistical power to detect a moderate effect of multivitamins on CD4 T-cell reconstitution. A major strength of our large observational cohort is the sample size afford detection of even modest effects on mortality, immunologic failure, and other clinical outcomes.

A randomized multivitamin dosing trial conducted in Tanzania by members of our team raised concern that multiple RDA multivitamins may increase the risk of hepatotoxicity, as indicated by elevated ALT, among HIV-infected adults on ART [16]. The mechanism of action by which multiple RDA multivitamins might elevate ALT in the presence of ART remains unknown. Nevertheless, in this observational cohort study, we found that single dose RDA multivitamins for ART-experienced adults and multiple RDA multivitamin appear to be safe in terms of hepatotoxicity. As a result, the benefits of these multivitamin doses appear to outweigh this potential risk.

This study has several limitations. First, due to the observational nature of the study we cannot rule out the risk of residual bias due to unmeasured confounding. Nevertheless, we attempted to minimize the potential for confounding by using rigorous statistical methods that included time-varying exposures and adjustment for numerous possible confounders, including allowing for non-linear continuous relationships with the outcomes. Second, our pharmacy database only included information on whether or not a patient received a bottle of multivitamins, but did not have data on adherence to the supplements. Accordingly, we likely underestimated the potential benefits of multivitamin supplements due to suboptimal adherence. Implementation studies on adherence counseling can guide strategies to maximize adherence to both multivitamins and ART. In addition, the MDH program used WHO HIV disease stage and

CD4 T-cell count criteria to determine ART eligibility during the study period. Therefore, our findings may not be directly generalizable to programs using a Test and Treat strategy where patients tend to patients initiate ART in a healthier state and at higher CD4 T-cell counts.

This implementation evaluation determined program provision of multivitamin supplements containing vitamins B-complex, C, and E was associated with improved survival, reduced incidence of TB and provided other clinical benefits for both ART-naïve and ART-experienced adults in Tanzania. A major strength of our study is that it represents real-world implementation of multivitamin supplementation program within a large HIV care and treatment program. The multivitamin program was scaled to over 50,000 participants during an 8-year period from 2004 to 2012. Randomized controlled trials may overestimate the programmatic impact of interventions due to selective recruitment criteria and intensified adherence and retention strategies. Overall, our results indicate that multivitamin supplementation appears to be a simple, low-cost, effective, safe, and scalable program to improve survival and health outcomes for HIV-infected receiving care in Tanzania and similar settings. Research is needed to determine the optimal composition and dosage of multivitamin supplements along with interventions to support adherence to both multivitamins and ART to maximize the potentially synergistic health benefits at scale.

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Table 1. Characteristics of 48,207 ART-naïve and 46,977 ART-experienced adult patients[1] enrolled in the HIV treatment and care program in Dar es Salaam, Tanzania from 2004 to 2012 at first multivitamin ascertainment (baseline).

Variable	**ART-naïve** % or Mean (SD) (N = 48,207)	**ART-experienced** % or Mean (SD) (N = 46,977)
Age, mean years	36.4 (9.7)	37.7 (9.6)
Male sex	29	30
Year		
- 2004 to <2006, %	4	9
- 2006 to <2008, %	24	32
- 2008 to <2010, %	46	39
- After 2010, %	27	20
District of Dar es Salaam		
- Ilala, %	28	39
- Kinondoni, %	38	33
- Temeke, %	34	28
Facility level		
- Hospital, %	85	84
- Health center, %	6	6
- Dispensary, %	9	10
Education		
- Primary, %	66	63
- Secondary, %	29	31
- Advanced, %	5	5
Marital Status		
- Married/cohabitating, %	50	49
- Single, %	13	13
- Widowed/divorced/separated, %	37	38
Body mass index (BMI), kg/m^2	21.9 (4.8)	21.6 (4.7)
Wasting (BMI <18.5 kg/m^2), %	24	25
CD4 T-cell count, cells/μL	281 (249)	192 (173)
Anemia (males Hb <13 g/dL, female <12 g/dL),	77	80
Severe anemia (Hb < 8.5 g/dL), %	18	17
Alanine aminotransferase (ALT) > 40 IU/L, %	11	13
Tuberculosis, %	11	12
WHO HIV stage		
- I, %	18	6
- II, %	23	15
- III, %	44	54
- IV, %	15	25
Multivitamin provision, %	86	59

[1]Patients can contribute follow-up visits to both ART-naive and ART-experienced periods.

Table 2. Association of multivitamin supplement provision with mortality and incident[1] health outcomes for HIV-infected ART-naïve adult patients in Management and Development for Health, Dar es Salaam, Tanzania from 2004 to 2012 (n=48,207)

		Unadjusted		Time-varying adjusted[5]	
Outcome	**Cases n (%)**	**Hazard Ratio[2] Estimate (95% CI)**	**p-value**	**Hazard Ratio[2] Estimate (95% CI)**	**p-value**
All-cause mortality	1,427 (3%)	0.54 (0.47- 0.62)	<0.001	0.69 (0.59- 0.81)	<0.001
ART eligibility[3]	8,413 (43%)	0.76 (0.71- 0.80)	<0.001	0.78 (0.73- 0.83)	<0.001
Incident anemia[4]	6,157 (56%)	0.67 (0.62- 0.71)	<0.001	0.90 (0.84- 0.97)	0.005
Incident severe anemia[4]	4,696 (12%)	0.61 (0.56- 0.65)	<0.001	0.92 (0.85- 1.00)	0.05
Incident wasting (BMI < 18.5 kg/m^2)	7,479 (21%)	0.66 (0.62- 0.70)	<0.001	0.81 (0.76- 0.86)	<0.001
Incident tuberculosis	4,347 (10%)	0.63 (0.58- 0.68)	<0.001	0.83 (0.76- 0.91)	<0.001
Incident WHO Stage III or IV	8,708 (44%)	0.61 (0.58- 0.65)	<0.001	0.73 (0.69- 0.78)	<0.001
Any increase in WHO HIV staging	15,031 (37%)	0.74 (0.71- 0.77)	<0.001	0.81 (0.77- 0.85)	<0.001
Incident ALT >40 IU/L	7,995 (19%)	0.71 (0.67- 0.75)	<0.001	0.90 (0.84- 0.96)	0.002
Incident ALT >200 IU/L	314 (<1%)	0.49 (0.37- 0.64)	<0.001	0.74 (0.55- 1.01)	0.06

[1] Individuals with event of interest at baseline excluded from the analysis

[2] Hazard ratio estimates compare patients who received multivitamins to the reference group of patients who did not

[3] Patients who were eligible for ART within 30 days of program enrollment were excluded from ART eligibility analysis

[4] Anemia: males Hb <13 g/dL, female <12 g/dL; severe anemia: <8.5 g/dL for both sexes

[5] Model adjusted for covariates with p-value < 0.2 in the univariate time to mortality models when covariate was not the outcome: age at baseline, sex, district, facility level, height, BMI, wasting at visit, MUAC at visit, CD4 cell count at visit, hemoglobin (Hb) at visit, anemia at visit, ALT at visit, tuberculosis at visit, WHO HIV stage, and on ART at within 60 days of enrollment. Time-varying analyses used updated covariates. Missing indicator method used for missing covariate observations in the adjusted models.

Table 3. Association of multivitamin supplement provision with mortality and incident[1] health outcomes for HIV-infected ART-experienced adult patients in Management and Development for Health, Dar es Salaam, Tanzania from 2004 to 2012 (n=46,977)

		Unadjusted		Time-varying adjusted[5]	
Outcome	**Cases n (%)**	**Hazard Ratio[2] Estimate (95% CI)**	**p-value**	**Hazard Ratio[2] Estimate (95% CI)**	**p-value**
All-cause mortality	4,790 (10%)	0.79 (0.75- 0.84)	<0.001	0.86 (0.80- 0.92)	<0.001
Incident anemia[3]	5,695 (64%)	0.84 (0.80- 0.89)	<0.001	0.83 (0.78- 0.88)	<0.001
Severe incident anemia[3]	4,418 (11%)	0.75 (0.70- 0.79)	<0.001	0.88 (0.82- 0.95)	0.001
Incident BMI < 18.5 kg/m^2	7,747 (22%)	0.83 (0.79- 0.87)	<0.001	0.83 (0.79- 0.88)	<0.001
Immunologic failure[4]	15,577 (36%)	0.71 (0.69- 0.73)	<0.001	0.70 (0.67- 0.73)	<0.001
Incident tuberculosis	4,642 (11%)	0.81 (0.76- 0.86)	<0.001	0.78 (0.73- 0.84)	<0.001
Incident WHO HIV Stage III or IV	3,709 (37%)	0.85 (0.79- 0.91)	<0.001	0.96 (0.88- 1.04)	0.27
Any increase in WHO HIV stage	5,516 (16%)	0.87 (0.83- 0.92)	<0.001	1.02 (0.95- 1.09)	0.62
Incident ALT >40 IU/L	10,267 (25%)	0.73 (0.70- 0.76)	<0.001	0.81 (0.77- 0.85)	<0.001
Incident ALT >200 IU/L	383 (<1%)	0.67 (0.55- 0.82)	<0.001	0.82 (0.65- 1.05)	0.12

[1] Individuals with event of interest at baseline excluded from the analysis
[2] Hazard ratio estimates compare patients who received multivitamins to the reference group of patients who did not
[3] Anemia: males Hb <13 g/dL, female <12 g/dL; severe anemia: <8.5 g/dL for both sexes
[4] Immunologic failure: On or after 168 days on ART, CD4 count ≤ CD4 at baseline, CD4 < half of the maximum value, or CD4 < 100 cells/µl.
[5] Model adjusted for covariates with p-value < 0.2 in the univariate time to mortality models when covariate was not the outcome: age at baseline, sex, district, facility level, height, BMI, wasting at visit, MUAC at visit, CD4 cell count at visit, Hb at visit, anemia at visit, ALT at visit, tuberculosis at visit, WHO HIV stage, and on ART within 60 days of enrollment). Time-varying analyses used updated covariates. Missing indicator method used for missing covariate observations in the adjusted models.