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Original article

# Lipid-based nutrient supplements containing vitamins and minerals attenuate renal electrolyte loss in HIV/AIDS patients starting antiretroviral therapy: A randomized controlled trial in Zambia

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SUMMARY

*Background & aims:* Advanced HIV infection combined with undernutrition and antiretroviral therapy (ART) places HIV/AIDS patients at high risk of electrolyte abnormalities and increased morbidity and mortality. Here, in a sub-study of a large published randomized trial, we evaluated if nutritional supplements will help curtail renal electrolyte loss in HIV/AIDS patients starting ART.

*Methods:* 130 malnourished HIV-positive patients referred for ART received lipid-based nutrient supplements alone (LNS, $n = 63$) or together with vitamins and minerals (LNS-VM, $n = 67$). Serum and spot urine samples were collected and assayed for creatinine, potassium, magnesium and phosphate concentrations at baseline and after 12 weeks of ART, and fractional excretion and reabsorption were calculated using standard equations.

*Results:* Eighteen (28.6%) patients from the LNS and 16 (23.9%) from LNS-VM groups died, most during the referral interval before starting ART. Phosphate excretion at baseline, was high in both LNS (mean ± SD: 1.2 ± 0.6 mg/mg creatinine) and LNS-VM (1.1 ± 0.8 mg/mg creatinine) groups relative to normal physiological ranges. Phosphate excretion remained high in the LNS group (1.1 ± 0.41 mg/mg creatinine) but significantly decreased in the LNS-VM group (0.6 ± 0.28 mg/mg creatinine; $p < 0.001$) after 12 weeks of ART. This difference is probably explained by increased renal tubular reabsorption of phosphate in the LNS-VM group (88.3 ± 5.7%) compared to the LNS group (76.6 ± 8.9%). The fractional excretion of potassium (FEK) was not significantly different at baseline between the two groups ($p = 0.69$) but the values were above normal physiological ranges (i.e. >6.4%) reflecting renal potassium wasting. However, FEK was significantly lowered in the LNS-VM group (6.2 ± 3.4%) but not in the LNS group (12.8 ± 4.7%) after 12 weeks of ART ($p < 0.001$). Finally, the fractional excretion of magnesium was not significantly different between the two groups at baseline ($p = 0.68$) and remained unchanged within normal physiological ranges at 12 weeks of ART ($p = 0.82$) in both groups.

*Conclusions:* The LNS-VM regimen appeared to offer protection against phosphate and potassium loss during HIV/AIDS treatment. This offers potential opportunities to improve care and support of poorly nourished HIV-infected patients in resource-limited settings.

*Trial registration:* www.pactr.org ID number: PACTR201106000300631.



*Abbreviations:* ART, antiretroviral therapy; eCcr, estimated creatinine clearance; FEK, fractional excretion of potassium; FEMg, fractional excretion of magnesium; GFR, glomerular filtration rate; LNS, lipid-based nutrient supplements; LNS-VM, lipid-based nutrient supplements with vitamins and minerals; NUSTART, nutritional support for Africans starting antiretroviral therapy; TRP, tubular reabsorption of phosphate.

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## 1. Introduction

With the massive scale-up of antiretroviral therapy (ART), HIV infection has been transformed from an incurable disease to a chronic disease; however, this is not without challenges [1,2]. In sub-Saharan Africa, a high number of HIV/AIDS patients starting ART die but the causes remain unclear [3]. A retrospective analysis of ~28,000 HIV-1 infected patient cohort in Zambia showed that mortality in the first 3 months of starting ART was significantly elevated among patients with body-mass index (BMI) less than 16.0 kg/m$^2$ compared to other BMI strata [4]. A number of factors including genetic influences, life style, malnutrition and ART have been attributed to the increased mortality. HIV infection, malnutrition and ART are known to contribute to renal tubular dysfunction resulting in life-threatening electrolyte loss [1,2,5,6]. For instance, malnutrition is linked to depletion or altered metabolism of vitamins and minerals [7]. Similarly, ART can exacerbate bone loss leading to electrolyte wasting [8]. Furthermore, clinical cases of renal proximal tubular dysfunction [6,9] including development of life-threatening renal Fanconi syndrome have been well documented with tenofovir-based ART use [2,10,11]. Fanconi's syndrome is the generalized dysfunction of proximal tubules in the kidney resulting in excessive loss of substances (e.g. phosphate, bicarbonate, amino acids, glucose, and low molecular weight proteins) in the absence of high plasma concentrations [12,13]. Consequently, the pathophysiological overlap of malnutrition, HIV infection and/or ART affect renal function that could drive clinically significant electrolyte losses. Hence, there is an urgent need for evidence-based interventions that may be employed to prevent or manage renal dysfunction linked to malnutrition and/or ART in HIV-infected patients.

Malnutrition is linked to depletion or altered metabolism of vitamins and minerals [7]. Published reports suggest that low serum phosphate concentrations in severely malnourished HIV-infected patients predicted early mortality [3]. Thus, in an effort to improve treatment outcomes a significant proportion of malnourished HIV-1 infected patients are now recommended to concurrently initiate ART with 'structured' nutritional supplementation [14]. Recent findings indicate that nutritional supplements coupled with vitamins and minerals significantly improve anthropometric measures [15]. However, there is a paucity of studies that have directly assessed whether supplements improve the homeostatic functions of the kidneys, for example, and curtail electrolyte loss. This was examined in the present study. The main objective was to measure the effects of nutrient supplements on kidney functions during the early phases of starting ART. Within this context, it was theorized that lipid-based nutrition supplements (LNS) with vitamins and minerals would curtail loss of electrolytes in HIV/AIDS patients initiating ART. For instance, normal phosphate homeostasis is balanced by daily phosphate intake and body excretion in the urine and feces. Both phosphate intake and excretion are modulated by the active metabolite of vitamin D (i.e. $1,25(OH)_2D_3$; also termed 'calcitrol') [16,17]. Specifically, calcitrol enhances phosphate uptake from the intestines and also fosters phosphate reabsorption in renal proximal tubules. Thus, nutritional supplements containing significant compliments of both phosphorous and vitamin D would be expected to curb phosphate excretion, in part, by promoting renal proximal tubular reabsorption of phosphates in the body. This notion and similar ideas pertaining to potassium and magnesium homeostasis were tested in the present study.

## 2. Materials and methods

### 2.1. Subject selection

One hundred and thirty HIV/AIDS patients aged between 18 and 49 years were enrolled in the study which was embedded in the Nutritional Support for Africans Starting Antiretroviral Therapy (NUSTART) trial [15,18]. Inclusion criteria were, ART-naive, BMI <18.5 kg/m$^2$, CD4 count <350 cells/μL or stage 3 or 4 disease, and not pregnant. The NUSTART study was conducted in Zambia and Tanzania. Patients for this sub-study were drawn from the Lusaka NUSTART site in Zambia based on recruitment between May and November 2013 but in all other respects were entirely representative of the whole trial population [18]. Participants were recruited to sequential identification (ID) numbers by clinic nurses who had no access to the study treatment codes. The randomization of subjects was done by the Data Safety and Monitoring Board statistician using a computer generated blocks of 16 randomization table stratified [18]. Fig. 1 shows the final subject distribution for the sub-study. The project was conducted towards the end of the parent NUSTART randomized clinical trial.

### 2.2. Intervention

The control research arm received lipid-based nutrient supplements (LNS), whereas the experimental arm was given LNS with minerals and vitamins (LNS-VM). The products were made for the trial by Nutriset (Malaunay, France) and they both contained 60% calories as fat and 10% calories as protein available in ready-to-eat packets [18]. LNS-VM also contained micronutrients mostly at 3 times the United Kingdom recommended nutrient intake for adult women [19], except iron that was at 1× recommended nutrient intake only in the second stage. By contrast, LNS contained vehicle and flavorings similar to LNS-VM but without added vitamins or minerals (see Table 1 for composition of supplements).

### 2.3. Study design

Patients received a stepped regimen of LNS or LNS-VM as described elsewhere [18]. Packages of LNS and LNS-VM were labeled with the study ID numbers by the clinic pharmacists at the time the packets were dispensed. Briefly, the supplementation started with small daily doses containing limited calories (30 g, 150 kcal), from time of referral for ART through the pre-ART

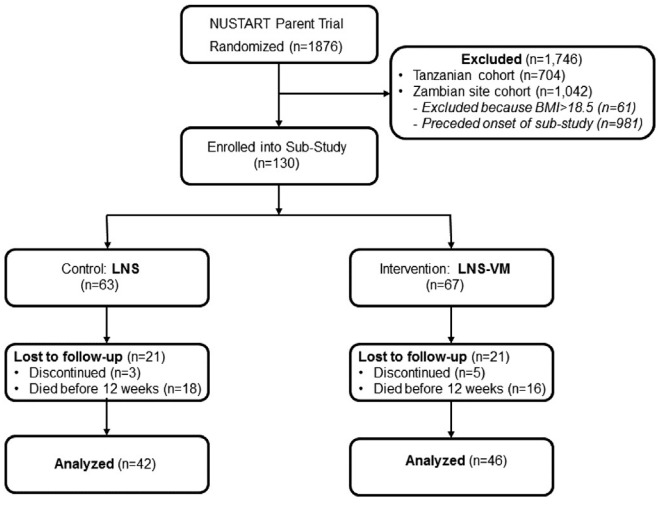


**Fig. 1.** Flow of the participants through the sub-study. Screening was limited to the Lusaka site in Zambia and involved all HIV-infected patients referred for CD4 testing and also had BMI <18.5 kg/m$^2$. Recruited patients were randomized in the parent NUSTART controlled trial. The sub-study was conducted towards the end of the parent NUSTART study. Abbreviations: LNS, lipid-based nutritional supplement; LNS-VM, lipid-based nutritional supplement with vitamins and minerals.