Nutritional Support for Africans Starting Antiretroviral Therapy

The NUSTART trial

Effects on mortality of a nutritional intervention for malnourished HIV-infected adults referred for antiretroviral therapy: a randomised controlled trial

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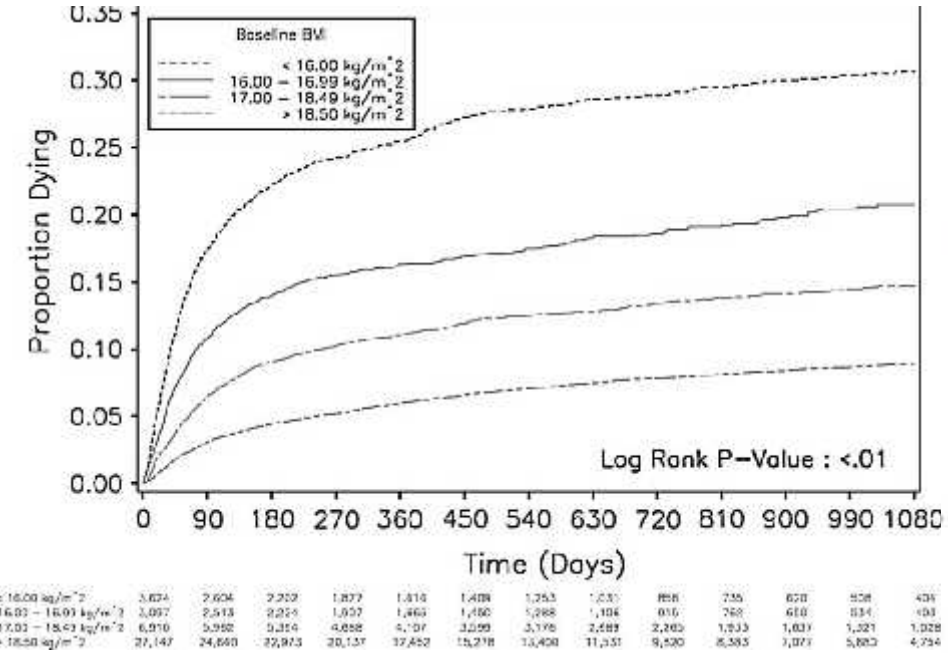
Rationale for the trial

- Early mortality when patients start ART is high
- Risk factors for mortality:
  - Advanced disease, i.e. very low CD4
  - Poor diagnosis and management of specific co-infections, especially tuberculosis
  - Low body mass index (BMI)

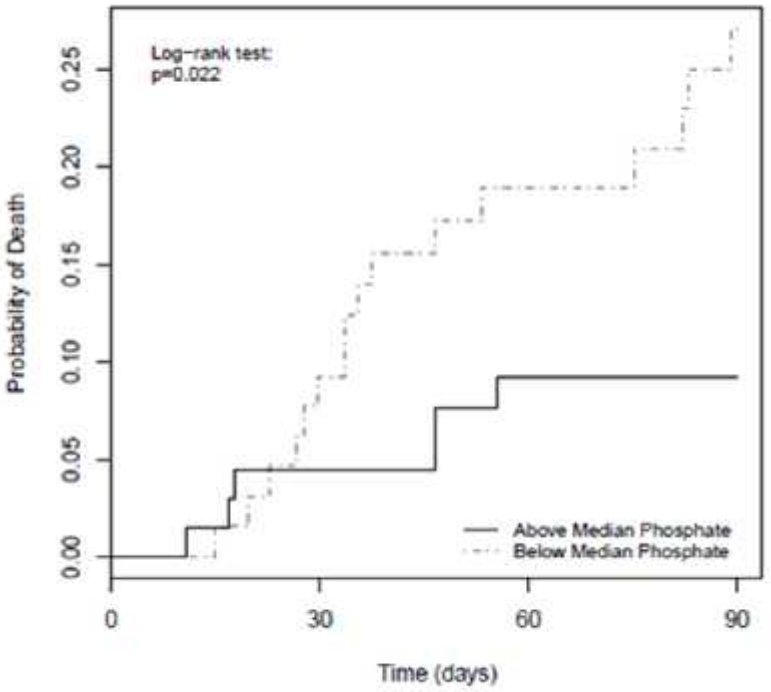
Nutrition and mortality of Zambian adults starting ART

Koethe et al., JAIDS 2009; Heimburger et al., PLoS One 2010; 5: e10687

Effect of low BMI



Effect of low serum phosphate



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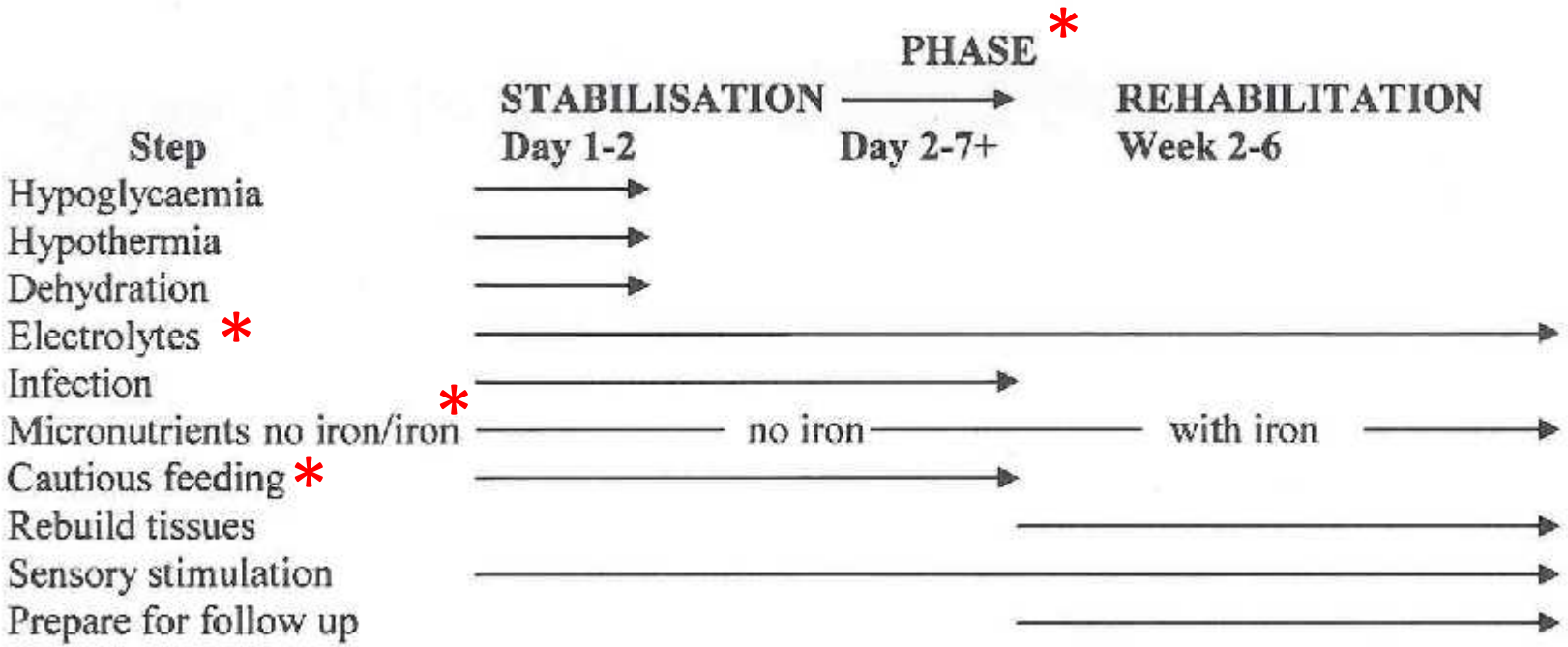
WHO 10 steps to managing severe malnutrition in children



A small prior study in Lusaka showed that both low BMI and low plasma phosphate were risk factors for mortality.

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NUSTART hypothesis

A nutritional intervention similar to that used for rehabilitation of severely malnourished children will:

- Decrease mortality from referral to ART until 12 weeks after starting ART (primary outcome)
- Decrease the incidence of adverse events from referral to ART until 12 weeks after starting ART
- Improve CD4 count by 12 weeks ART

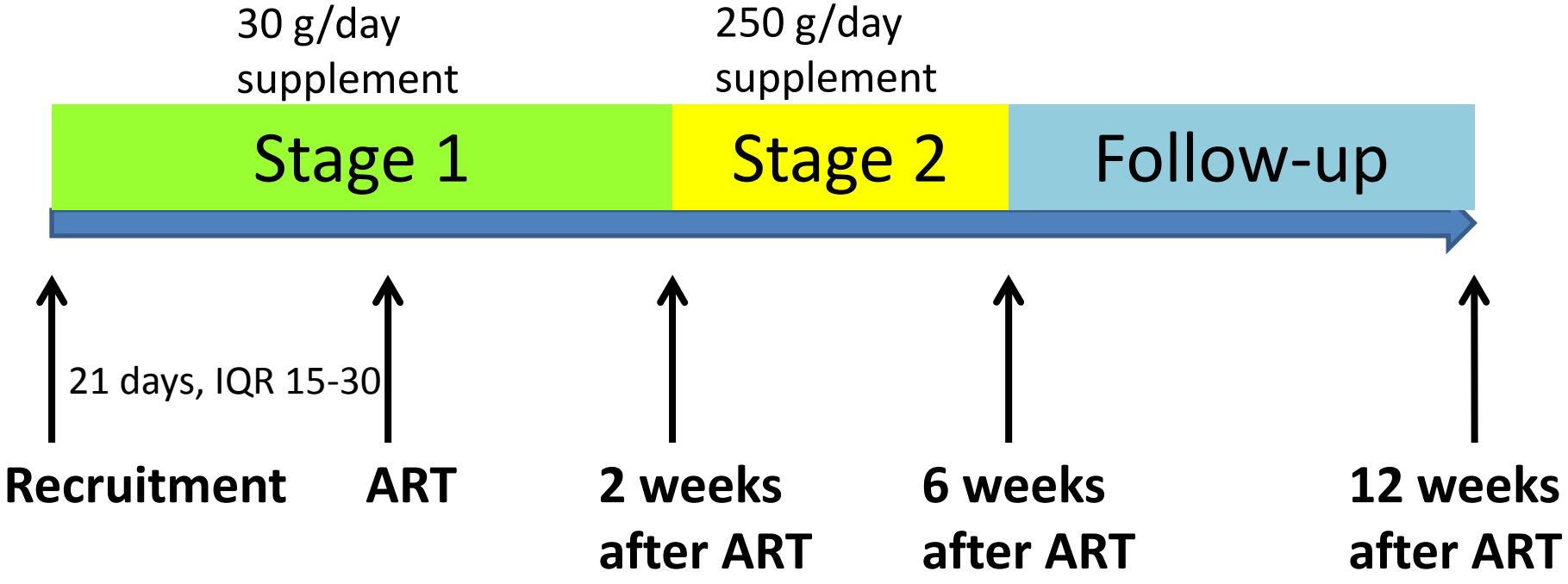
NUSTART design

- Randomised controlled phase III trial of vitamins and minerals in a 2-stage protocol:

  Stage 1. Stabilization: high vitamins and minerals (no iron) but low calories

  Stage 2. Rehabilitation: high vitamins and minerals (including iron) with high calories

- Intervention products: lipid-based nutritional supplements without (**LNS**) or with vitamins and minerals (**LNS-VM**)



Intervention product composition – amounts per day[1]

Nutrient	First phase supplement (from recruitment to 2 weeks of ART)		Second phase supplement (from 2 to 6 weeks of ART)	
	LNS-VM (30 g)	LNS (30 g)	LNS-VM (250 g)	LNS (250 g)
Calories (kcal)	100	100	1360	1360
Retinol (as palmitate) (mg)	1800	0	1800	0
Vitamin D (mg)	10	0	10	0
Vitamin E (mg)	45	0	45	0
Vitamin K (mg)	95	0	95	0
Vitamin C (mg)	120	0	120	0
Thiamin (mg)	2.4	0	2.4	0
Riboflavin (mg)	3.3	0	3.3	0
Niacin (mg)	39	0	39	0
Pyridoxine (mg)	3.6	0	3.6	0
Folate (mg)	600	0	600	0
Vitamin B12 (mg)	4.5	0	4.5	0
Pantothenic acid (mg)	9	0	9	0
Zinc (as sulphate) (mg)	21	0	21	0
Copper (mg)	3.6	0	3.6	0
Selenium (mg)	180	0	180	0
Manganese (mg)	4.2	0	4.2	0
Chromium (mg)	75	0	75	0
Iodine (mg)	420	0	420	0
Iron (as sulphate) (mg)	0	0	14.8	0
Potassium (as KH_2PO_4) (mmol)	64	0	64	0
Phosphorus (as KH_2PO_4) (mmol)	48	0	48	0
Magnesium (as sulphate) (mmol)	24.8	0	24.8	0

Intervention supplement

NUSTART inclusion and exclusion criteria

Inclusion

- Resident in the clinic catchment areas in Mwanza, Tanzania and Lusaka, Zambia
- 18 years old and above
- BMI < 18.5 kg/m^2
- ART naive
- Requiring ART (CD4 < 350/ml or WHO stage 3 or 4)
- Willing to consent

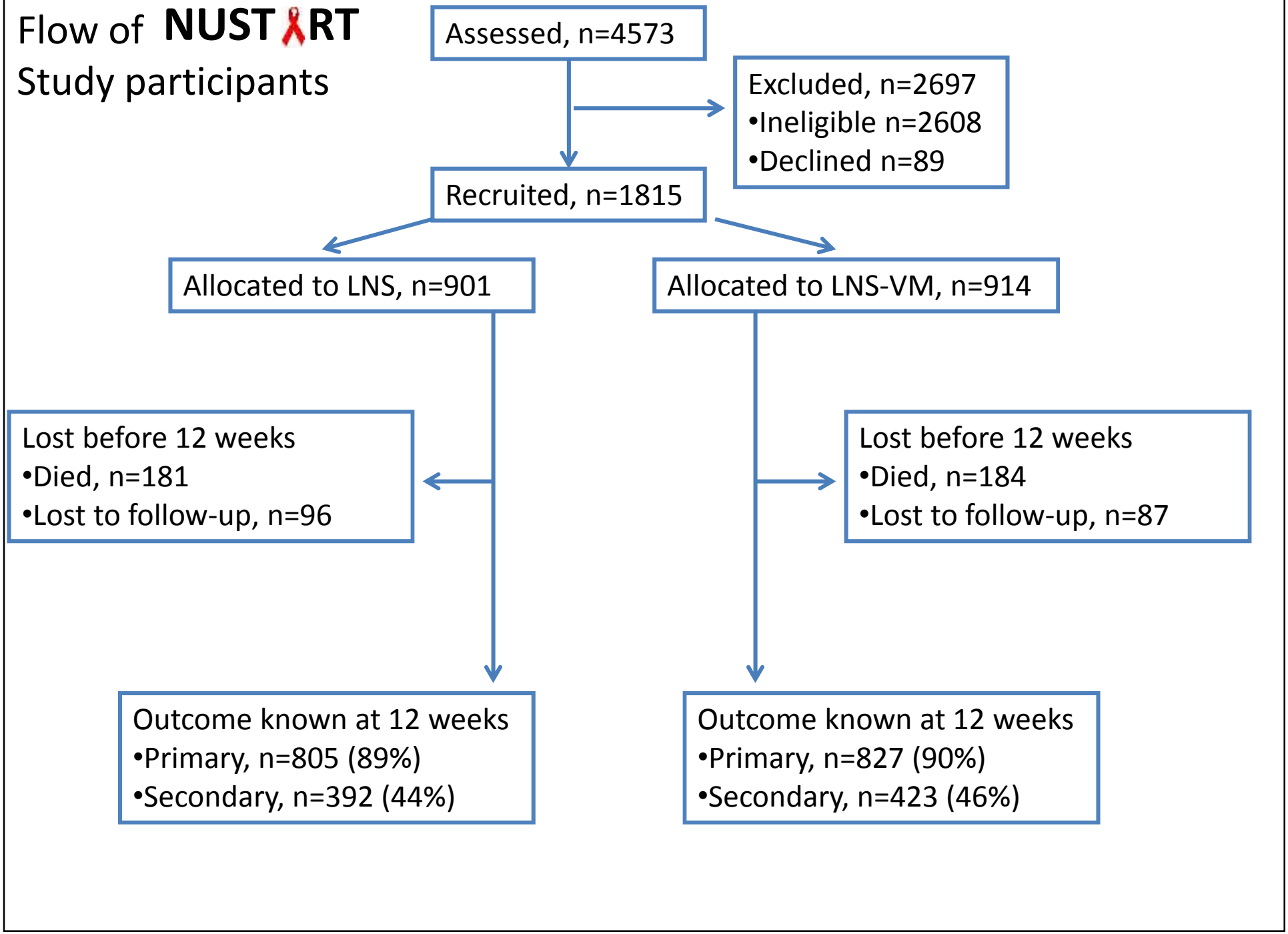
Exclusion

- Pregnant by self-report

Sample size

- Planned 2300 based on decreasing mortality by 33% from 30/100-person-years in the control group
- Mortality was much higher than expected so, after DSMB interim analysis, stopped recruitment at 1815

Flow of NUSTART Study participants

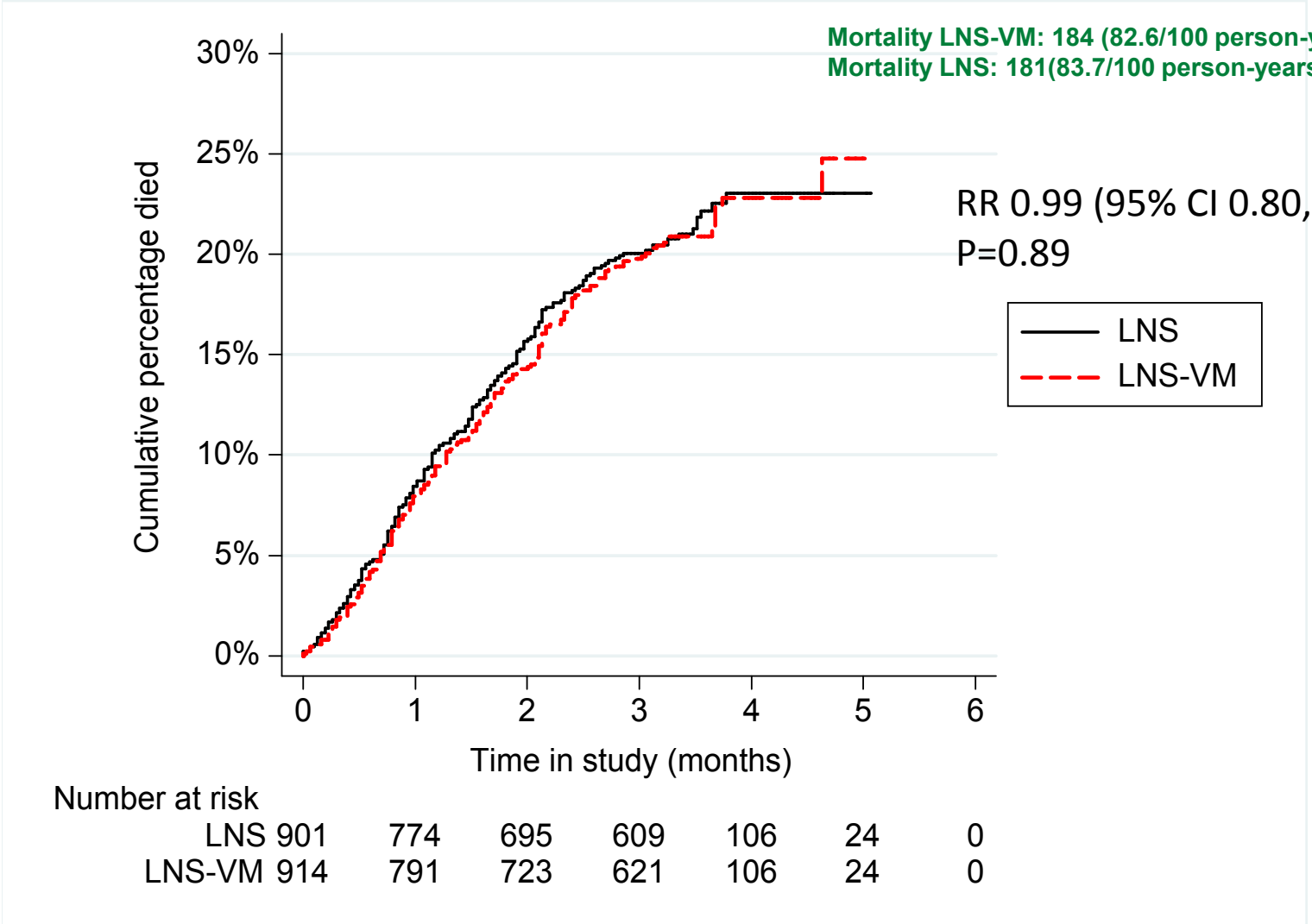


Description of NUSTART population

	LNS-VM, n=914	LNS, n=901
% female	49%	51%
Age (y)	35.9 (SD 9.4)	35.7 (SD 9.4)
BMI (kg/m^2)	16.4 (SD 1.4)	16.4 (SD 1.4)
% BMI < 17 kg/m^2	59%	59%
CD4 count (cells/㎖)	134 (SD 97)	139 (SD 103)
Hb (g/L)	95 (SD 23)	97 (SD 24)
% phosphate < 0.87 mmol/L	12%	9%
% Oedema at baseline	3%	4%
% on TB treatment pre-ART	28%	22%

Effect of intervention on mortality

overall mortality rate = 83/100 person-years



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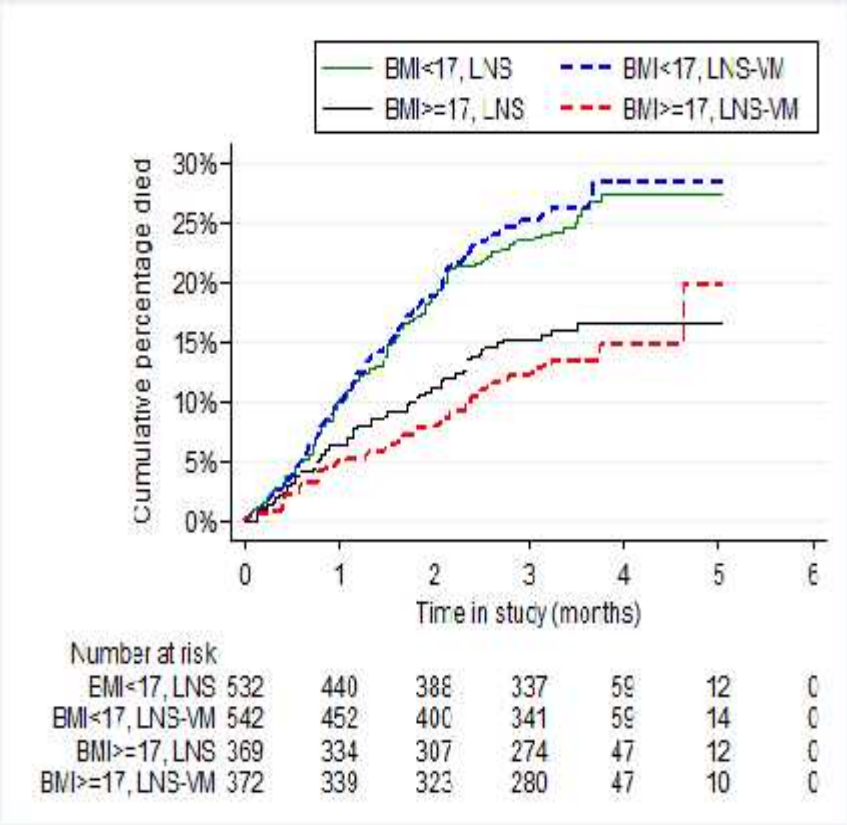
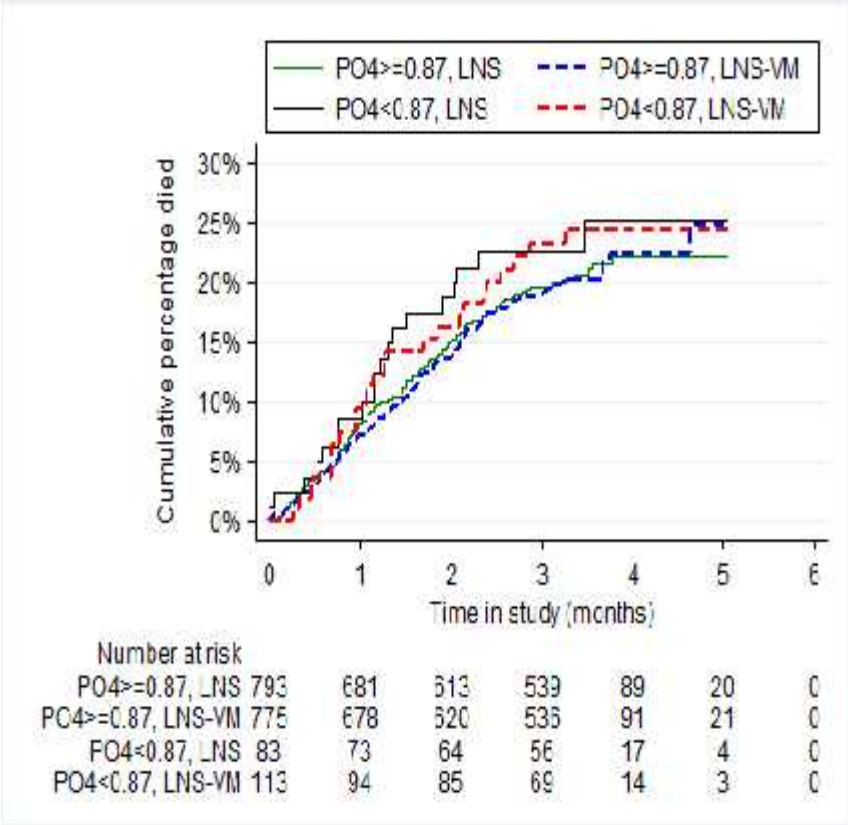
Planned stratified analyses of mortality

Stratified by BMI </> 17 kg/m²



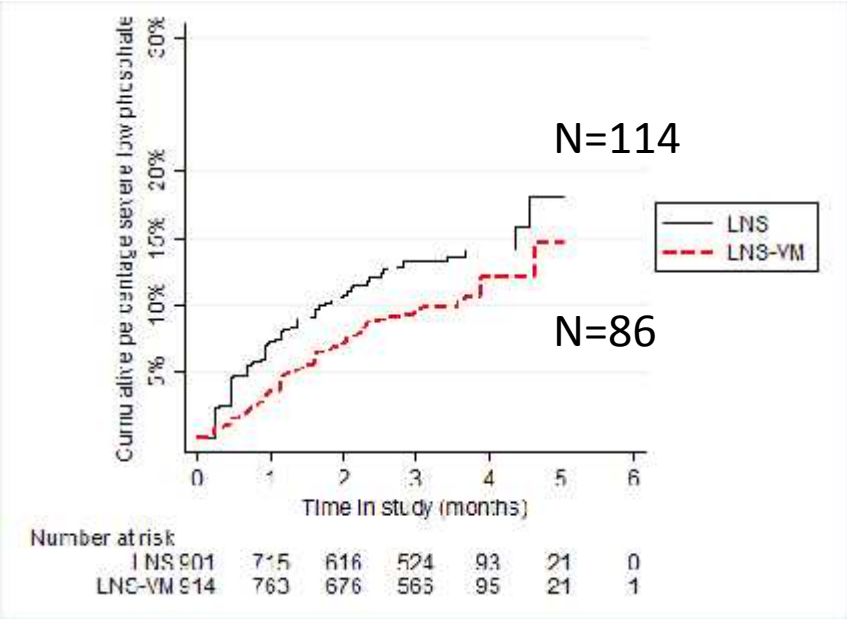
Stratified by PO4 </> 0.87 mmol/l



Effect of intervention on severe low electrolyte adverse events (DAIDS)

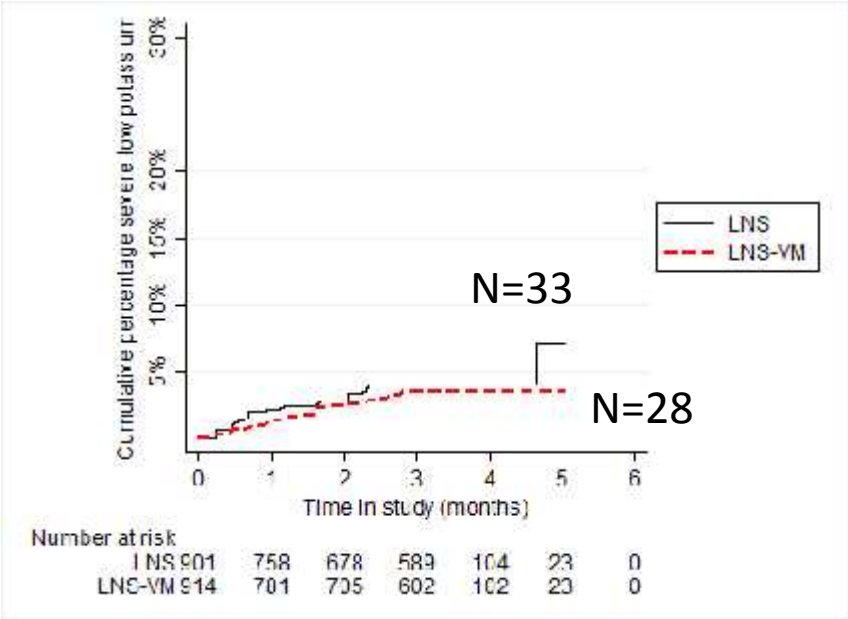
Plasma phosphate <0.65 mmol/L

RR 0.73 (95% CI 0.55, 0.97) P=0.03



Plasma potassium <2.5 mmol/L

RR 0.82 (95% CI 0.50, 1.36) P=0.44



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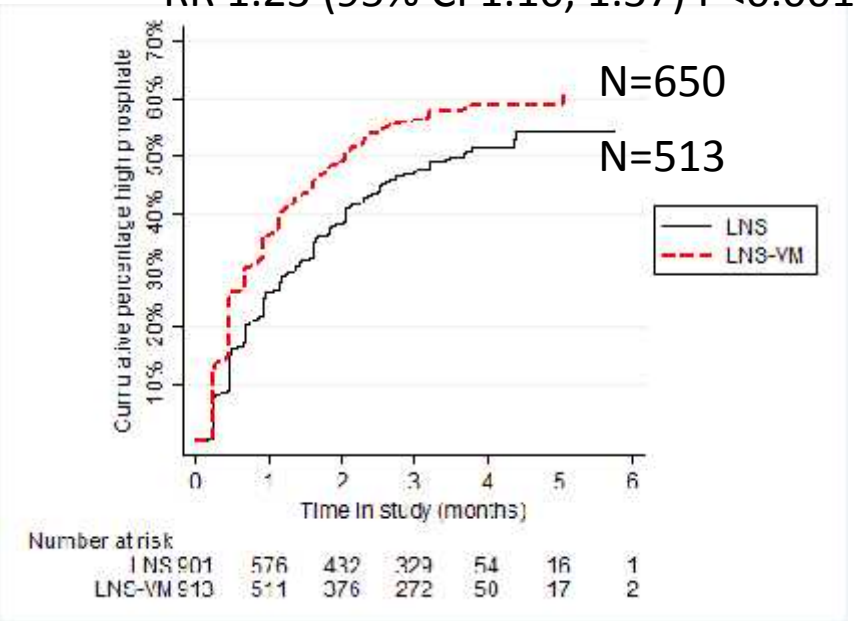
Effect of intervention on high electrolyte adverse events

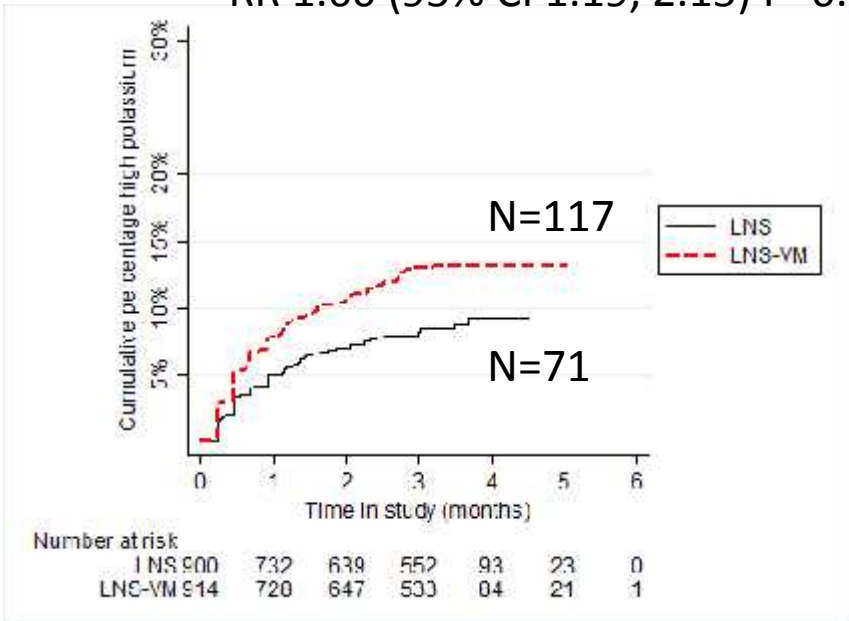
Plasma phosphate >1.45 mmol/L

RR 1.23 (95% CI 1.10, 1.37) P<0.001



Plasma potassium >5.5 mmol/L

RR 1.60 (95% CI 1.19, 2.15) P=0.002



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Effect of intervention on CD4 count at 12 weeks adjusted differences, LNS-VM versus LNS

CD4 (cells/mL)	LNS-VM	LNS	Adjusted difference (95% CI)	P
All baseline	134 (SD 97)	139 (SD 103)		
Completers at baseline	144 (SD 99)	153 (SD 101)		
12 weeks	297 (SD 188)	280 (SD 154)	25 (4, 46)	0.02

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Conclusions

- The trial intervention:
  - had no effect on the primary outcome of mortality,
  - increased CD4 counts,
  - decreased risk of low phosphate but increased risk of high phosphate and potassium.
- The treatment of patients presenting with low electrolytes and the increased risk of high electrolytes in the LNS-VM group may have interfered with testing the part of the hypothesis related to low phosphate.

Thank you