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HIV-INFECTED CHILDREN WITH SEVERE ACUTE MALNUTRITION EARLY VERSUS DELAYED ART INITIATION

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Introduction

HIV-infected children with severe acute malnutrition (SAM) represent a distinct clinical entity characterized by a complex interplay between increased energy expenditure with an increased basal metabolic rate, higher rates of co–infections, diarrhea and malabsorption, increased micronutrient deficiencies and higher rates of food insecurity and poverty. Management is complicated by gastro–intestinal side effects to antiretroviral drugs, perturbed lipid and glucose metabolism, and altered pharmacokinetics of ART and antibiotics.

Despite nutritional rehabilitation, the CD4 counts in HIV–infected severely malnourished children continue to decline, and they have a three–fold higher probability of mortality compared to their non-infected counterparts. Although ART in HIV infected children has significantly improved survival and quality of life, SAM remained an independent predictor of mortality even with appropriate immunologic and virologic responses to ART.

In 2010 the World Health Organization's (WHO) Nutrition Guideline Advisory Group identified determining the optimal timing of ART initiation and ART dosing for HIV–infected children with SAM as a key issue for which guidance must be developed.

Aims

To compare the nutritional, immunological and virological responses to ART at 48 weeks in HIV infected severely malnourished children started immediately on HAART versus children in whom HAART is delayed until their severe malnutrition is resolved

Materials and methods

Subjects were enrolled from King Edward VIII Hospital, a referral hospital in Durban, South Africa. The key inclusion criteria were:

- Severe acute malnutrition (Weight/Height < -3 Z score or Mid-upper arm circumference < 11.5cm or Pedal Oedema)
- HIV infected diagnosed as per South African National guidelines and no prior ART exposure (except for PMTCT)

Subjects were randomised to an early treatment arm (initiation of ART within 14 days of admission to hospital) or delayed treatment arm (initiation of ART after nutritional recovery and after 2 weeks following admission)

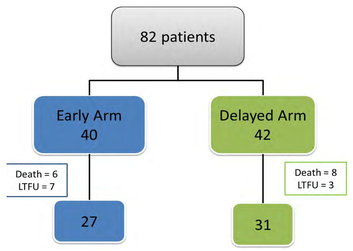
Management of the SAM was as per the WHO Inpatient Management of SAM protocol[4]. Subjects were initiated on Abacavir, Lamivudine and Lopinavir/rtv if <3yrs of age/<15kg or Abacavir, lamivudine and Efavirenz if >3yrs of age />15kg. All doses were prescribed using the weight-band dosage chart as per the South African National Guidelines (based on the WHO weight-band dosage chart)[5].

Patients were followed up at baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks and 48 weeks during which a history, clinical examination, anthropometric examination (weight, length/height, occipito-frontal circumference, mid-upper arm circumference, Skin fold thickness over the triceps and sub-scapula) was performed.

In addition CD4 counts, HIV Viral loads and safety bloods were performed at each of the above time-points. A 12 hour pharmacokinetic study was performed at day 1 and day 14 after initiation of ART.

Results

A total of 82 patients were enrolled in the study, 40 in the early arm and 42 in the delayed arm. At week 48, in the early treatment arm 27 patients (68%) completed follow-up (six deaths and seven lost to follow-up (LTFU)) while in the delayed arm 31 patients (74%) completed follow-up (eight deaths, three LTFU)



ABSTRACT

Background:
Poor access to HIV diagnostic testing and ART services for children from low and middle-income countries, frequently results in malnutrition at initial presentation. Despite ART initiation, HIV positive children with malnutrition have a higher mortality and delayed immune recovery. The optimal timing of ART initiation in children with malnutrition has not been established.

Methods:
Eighty-two HIV infected children with severe acute malnutrition (SAM) admitted to King Edward VIII Hospital between July 2012 and December 2015 were enrolled. Patients were randomized to initiate ART within 14 days from admission (Early arm) or delay ART initiation until nutritional recovery and more than 14 days from admission (Delayed arm). All patients received a standardized treatment and feeding protocol and were evaluated at 4, 8, 12, 24 and 48 weeks.

Findings:
The average age of the patients at baseline was 23·3 months (SD 27·9, range 1.6–129 months). The mean time from admission to ART initiation was 5·6 days (SD 4·4) in the early arm and 23 days (SD 5·8) in the delayed arm (p<0·001).
There was no significant difference in mortality (p=0·621), virologic response (p=0·527) and anthropometric response (p= 0·566) between the two groups at 48 weeks. However the rates of change in CD4, viral load, WAZ and HAZ scores occurred earlier and favored the delayed arm.

Patient Characteristics at baseline

Time from admission to ART initiation
(p<0·001) i.e. mean of 5·6 days (SD 4·4) in the early arm and
23 days (SD 5·8)
in the delayed arm

	Early	Delayed	p value
Total number (82)	40	42	
Age (months)	25·7 (1·7–129)	21·1 (1·6–99·7)	0·64
Gender (M:F)	60%(24): 40%(16)	55%(23): 45%(19)	0·52
CD4 Abs (mean)	805	952	0·59
CD4 % (mean)	16·4	18%	
ABC/3TC/EFV	12·2% (10)	11·9% (5)	0·35
ABC/3TC/LPV/rtv	87·8% (30)	88% (37)	
Time to ART initiation (days)	5·6	23	0·0001
Tuberculosis at baseline	38% (16)	35·7% (15)	0·49
WAZ (mean)	-3·518	-3·35	0·54
WHZ (mean)	-2·217	-2·17	0·36
MUAC (mean)	11·36	11·7	0·66
Hb (admission)	8·87	8·8	0·37
TP (mean)	66	65	0·44
Alb (mean)	22·47	23·8	0·66

Mortality

•During the 48-week study period 14 patients (17%) demised, six (15%) in the early arm and eight (19%) in the delayed arm. The difference in the mortality between the two arms was not statistically significant (p=0·626). The average time from enrollment to death was 74·4 days (SD: 59·9), range 12–252 days. The mean time to death was 92·7 days in the early arm compared with 60·8 days in the delayed arm. No patient demised prior to ART initiation. The majority (78·6%) of deaths occurred before 12 weeks, 67% and 87·5% in the early and delayed arms respectively.

CD4 count

•There was a significant increase in the overall mean CD4 count from a baseline count of 878·5 cells/uL (SD 772·8) to 1447·9 cells/uL (SD 739·0) at 48 weeks (p–value=0·001). The mean CD4 count at week 48 was 1366·7 (SD 732·4) cells/uL in the early arm and 1518·2 (749·8) cells/uL in the delayed arm (p=0·532)

•Comparison of the change in CD4 count using a multiple mixed effects linear regression model (Figure 2) suggested no statistically significant difference in immune recovery between the two groups.

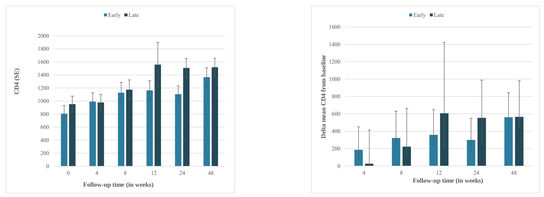


Figure 2: (a) Mean CD4 and (b) delta mean CD4 from baseline by trial arm and time point

Viral Load

•At 24 weeks, 67·3% of combined patients achieved protocol define response (VL <1000 copies/ml) overall, 59·7% in the early arm compared to 75% in the delayed arm (not statistically significant). By 48 weeks the number of patients with protocol defined virologic response increased to 81·1% overall, 77·8% in the early arm and 84%[5] in the delayed arm. This difference at 48 weeks was not statistically significant before and after multivariable adjustment (OR=1·66, p=0·527, 95% CI 0·34–8·06).

•A multiple mixed effects linear regression model evaluating viral load endpoint and change, favored the delayed arm at 24 and 48 weeks.

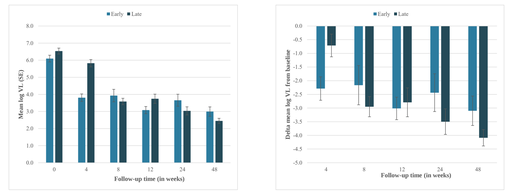


Figure 3: (a) Mean log VL, (b) delta mean VL from baseline by trial arm and time point

Anthropometry

•At week 48, 76·6% of patients achieved an adequate anthropometric response, with similar responses in both arms (77·2% in early arm and 76·6% in the delayed arm (p= 0·918)). The adjusted comparison of anthropometric response at week 48 was not significant (OR=1·66, p=0·566, 95% CI 0·29–9·31)

•There were no significant differences in BMIZ or WHZ scores between the two arms at 48 weeks (OR=0·79, p=0·43, 95% CI –0·96–2·25). At week 48 the difference in weight for age Z-score (WAZ) between the two arms was marginally significant (OR=1·67, p=0·094, 95% CI 0·11–1·44) whilst the difference in height for age Z-score (HAZ) was statistically significant (OR=2·51, p=0·012, 95% CI 0·27–2·25). (Figure 4). After adjusting for age, gender, immune stage, tuberculosis, haemoglobin (Hb), total protein (TP) and albumin (Alb), only the change in HAZ remained marginally significant.

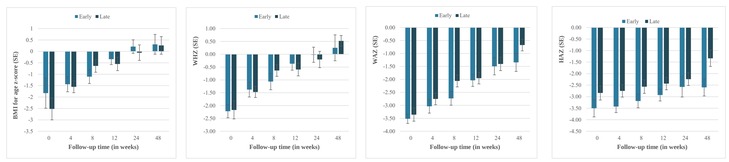


Figure 4: (a) Mean BMI for age z-score, (b) Mean Height-for-age z-score (HAZ), (c) Mean Weight-for-age (WAZ) z-score and (d) mean Weight-for-height z-score (WHZ) by trial arm and time point

Conclusions

HIV–infected children admitted with SAM and initiated on ART demonstrated significant improvements in CD4 counts and anthropometric parameters, together with significant viral load reduction compared to baseline. In this randomized controlled trial comparing early versus delayed ART initiation in HIV infected children admitted with SAM, although the differences in CD4 count, viral suppression and anthropometric response at 48 weeks was not significant, the rates of change in CD4, viral load, WAZ and HAZ scores occurred earlier and favored the delayed arm. Based on the results of this study, we recommend that ART initiation in children with SAM should be delayed for at least two weeks after starting nutritional rehabilitation.

Conflict of Interest

The authors declare no conflict of interest.

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