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Acute kwashiorkor soon after initiating ART among HIV infected children in the ARROW (AntiRetroviral Research fOr Watoto) trial

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BACKGROUND

- There are anecdotal reports of acute kwashiorkor developing soon after initiation of anti-retroviral therapy in resource-limited settings among HIV-infected children, where large numbers have moderate to severe chronic malnutrition
- We present findings from 1,207 children participating in the ARROW trial in Zimbabwe and Uganda.

METHODS

- ARROW is a randomised trial of monitoring and first-line treatment strategies. Children are started on ART (Abacavir, Lamivudine, Nevirapine or Efavirenz ± Zidovudine) at enrolment, and are assessed every 4 weeks
- Comparison of baseline characteristics between children admitted to hospital within 12 weeks of starting ART with severe oedematous malnutrition, admitted with non-oedematous malnutrition, or not admitted
- Case note review of admissions with severe oedematous malnutrition
- Comparison between groups of change in CD4 at 12 weeks, mortality at 28 weeks, growth from baseline to 28 weeks.

RESULTS

During the first 12 weeks on ART, 38 of 1,207 (3%) ARROW children were admitted to hospital with severe malnutrition, of whom 19 (50%) had oedematous malnutrition (kwashiorkor); incidence of oedematous malnutrition 7/100 child-years [95% CI 4.2, 10.9]; none of these children had oedema at baseline

- Median time from ART initiation to hospital admission for children with marasmus (severe wasting) was 28 days (IQR 14, 36), and 24 days (IQR 14, 56) for children with kwashiorkor

Baseline characteristics

- At baseline, children hospitalised with kwashiorkor were older and more severely immunocompromised than those with marasmus (table 1)
- 13/221 (6%) children with baseline weight-for-age and CD4% Z-scores <-3 developed acute oedematous malnutrition
- No significant differences across groups in primary carer, or in the percentage of household income spent on food (median 25%, IQR 10, 45).

Table 1. Baseline characteristics prior to ART initiation

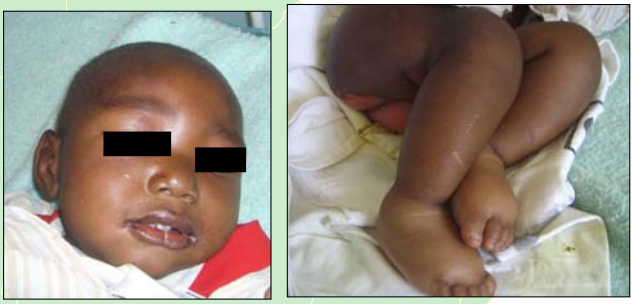
	Not hospitalised N = 1,169	Hospitalised with Marasmus Post ART N = 19	Hospitalised with Kwashiorkor Post ART N = 19	P value
Age in years Median (IQR)	6 (2, 9)	2 (1, 8)	6 (2, 8)	0.05
CD4% Median (IQR)	12 (8, 18)	10 (8, 15)	3 (1, 14)	<0.01
Weight-for-age Z score Median (IQR)	-2.1 (-3.2, -1.2)	-4.6 (-6.0, -4.0)	-4.8 (-6.2, -3.6)	<0.01
Height-for-age Z score Median (IQR)	-2.4 (-3.3, -1.4)	-3.2 (-4.0, -2.3)	-3.3 (-4.2, -2.5)	<0.01
MUAC[1] <11cm No. (%)	30 (2.6%)	4 (21.0%)	4 (21.0%)	<0.01
MUAC <12.5cm No. (%)	145 (12.4%)	12 (63.2%)	9 (47.3%)	<0.01

[1] MUAC = mid upper arm circumference

Case note review - clinical features of oedematous malnutrition after ART

- The onset of oedema was progressive, and associated with increased skin fragility (Figure 1)
- 9/19 (47%) had concomitant pneumonia or tuberculosis; only 2 had a history of chronic diarrhoea
- All children had normal renal and hepatic function; serum albumin was low in all patients in whom it was measured (n=10).

Figure 1. Facial oedema, pedal oedema & extensive perineal skin loss 2º to napkin dermatitis in 15 month-old child on ART



Follow-up

- The increase in CD4% was similar among hospitalised and non-hospitalised children (table 2). However, baseline CD4% was lower among the kwashiorkor cases, so their relative increase was significantly higher (200%) than those with marasmus (80%) or with non-hospitalised patients (75%)
- High mortality occurred among those admitted; 6/19 (32%) children with marasmus and 3/19 (16%) children with kwashiorkor had died by 28 weeks after ART initiation
- Children who survived recovered well (table 3), the increase in Weight for Age and MUAC from baseline was significantly greater in those with kwashiorkor or marasmus compared to non-hospitalised patients.

Table 2. Change in CD4 from baseline to 12 weeks

Median (IQR)	Not hospitalised N = 1,169	Hospitalised with Marasmus Post ART N = 19	Hospitalised with Kwashiorkor Post ART N = 19	P value
Increase in CD4%	+8 (4, 12)	+8 (3, 11)	+7 (3, 11)	0.7
Relative increase, CD4%	75% (37, 139)	80% (52, 132)	200% (50, 500)	0.04

Table 3. Growth from baseline to 28 weeks among survivors

Median change (IQR)	Not hospitalised N = 1,146*	Hospitalised with Marasmus Post ART N = 13	Hospitalised with Kwashiorkor Post ART N = 16	P-value
Weight-for-age Z score	+0.4 (0, 1.0)	+1.9 (0.6, 2.4)	+2.2 (1.5, 3.5)	<0.01
Height-for-age Z score	+0.4 (-0.2, 0.3)	-0.3 (-0.6, 0.5)	+0.0 (-0.3, 0.2)	0.9
Change in MUAC (cm)	+0.9 (0.1, 1.9)	+2.4 (1.2, 4.0)	+3.9 (2.6, 4.5)	<0.01

* Children surviving 28 weeks

CONCLUSIONS

- In other published case series from Uganda and Malawi, children with marasmus prior to ART initiation were significantly more immunocompromised than those with oedema which is the reverse of the post-ART situation described here
- The profound baseline immunosuppression, severe wasting, marked increase in CD4% and timing of oedema suggest a possible aetiological role for immune reconstitution inflammatory syndrome (IRIS) in children hospitalised with severe oedematous malnutrition shortly after ART initiation
- Children in ARROW have blood samples taken at baseline, 4 and 12 weeks for immunophenotyping to ascertain T cell immune activation status, which may shed further light on underlying immunological mechanisms.

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