Weight gain in children initiating ART is not increased by nutritional supplements

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ABSTRACT

Background: Malnourished HIV-infected children in resource-limited settings is common, but rapid weight gain usually follows ART initiation. The effect of ready-to-use therapeutic foods (RUTF) in this context is unclear. The nutritional status of a child is likely to influence both the use and effect of RUTF, so causal models are required to establish benefit.

Methods: ARROW is an ongoing randomised trial of monitoring and treatment strategies in ART-naive children in Uganda/Zimbabwe. Enrollment was from May 2007 to November 2008; nutritional supplement data was collected from December 2007. Three of four centres gave Plumpy'nut, a peanut-based RUTF, using criteria that included weight-for-height; mid-upper arm circumference, clinical status and knowledge of food insecurity. Marginal structural models with time-dependent inverse probability treatment weights were used to estimate the causal effect of Plumpy'nut on weight-for-age Z-score (WAZ) over the first 48 weeks on ART among children aged ≥5 years who were enrolled after December 2007, stratifying by centre to compute weights.

Results: 387 children aged ≥5 years at ART initiation were enrolled from the 3 centres after Dec 2007: 207 (53%) were female, median (IQR) age 3.1 (2.0)-5.0 years, weight-for-age Z-score 1.0 (-2.9, 0.8), height-for-age Z-score 0.8 (-2.4, 1.2). Weight-for-height Z-score 2.0 (-4.6, 5.2); Plumpy'nut was used by 66 (17%) children for median (IQR) 17 (0,36) weeks, starting 22 (6) weeks after enrolment. Time-dependent prediction of Plumpy'nut use were age, WAZ, weight -60% expected, mid-upper arm circumference and previous hospital admission. Children given Plumpy'nut had lower WAZ at baseline (-0.4 (0.4-1.0), p<0.05). In unadjusted analysis, median improvement in WAZ at 48 weeks was greater among those receiving Plumpy'nut (+0.5 vs +0.1); however the reflected greater weight gain in children starting from very low WAZ regardless of Plumpy'nut use. In adjusted analysis, the causal effect of Plumpy’nut was small and not statistically significant (+0.2 per month (95%CI 0.0-0.4, p=0.04).

Conclusions: Malnourished HIV-infected children initiating ART plus RUTF generally experience rapid weight gain. However, a marginal structural model applied to observational data with time-varying confounders suggests that the weight gain cannot be attributed to the use of RUTF. Future use of RUTF for stable, malnourished children entering ART programs may therefore not be clinically beneficial.

RESULTS

1208 children enrolled to ARROW

- 66 children (17%) given RUTF during first 48 weeks of ART - started median 2 weeks after enrolment (IQR 2,8) - Children enrolled before 1 Dec 2007: RUTF use not recorded before this date, n=225

367 children eligible for analysis of RUTF and weight gain

- Baseline characteristics:
  - Sex: boys n (%): 198 (56%)
  - Age years median (IQR): 3.3 (1.6, 6.1)
  - WHO stage: n:
    1.  n (%) 10 (3%)
    2.  141 (39%)
    3.  159 (44%)
    4.  67 (17%)
  - CD4%: <5 yrs median (IQR): 15% (11%, 20%)
  - CD4%: 5 yrs median (IQR): 280 (122, 500)
  - Weight-for-age z-score median (IQR):
    1.  -1.9 (-2.8, -1.0)
    2.  -2.4 (-3.4, -1.3)

- Children aged 10 years before 48 weeks follow-up - normalised data unavailable, n=327

- One trial site provided nutritional support externally - incomplete supplement data, n=267

- Children enrolled before 1 Dec 2007: RUTF use not recorded before this date, n=225

RUTF and WEIGHT GAIN – unadjusted analysis

- 66 children (17%) given RUTF during first 48 weeks of ART - started median 2 weeks after enrolment (IQR 2.8) - continued for median 17 weeks (IQR 6.30)

- Baseline WAZ lower in children given RUTF:
  - 4.0 vs -1.5 in users and non-users, respectively

- Greater WAZ increase in children given RUTF:
  - +2.0 vs +0.5 in users and non-users, respectively

RUTF and WEIGHT GAIN – adjusted analysis

- 387 children eligible for analysis of RUTF and weight gain

- Excluding children aged 10 years before 48 weeks follow-up - normalised data unavailable, n=327

- One trial site provided nutritional support externally - incomplete supplement data, n=267

- Children enrolled before 1 Dec 2007: RUTF use not recorded before this date, n=225

- Greater WAZ increase in children given RUTF:
  - +2.0 vs +0.5 in users and non-users, respectively

SUMMARY

Children showed excellent growth during their first year on ART. However, causal modelling suggests that RUTF does not significantly increase weight gain in children initiating ART. Children given RUTF did have greater increases in weight-for-age, but marginal structural modelling showed that this association was not causal. Growth reconstitution in HIV-infected children appears to be mediated primarily by ART. The results of this observational analysis should be confirmed with a randomized trial of RUTF. The REALITY trial, starting in 2012, will include ready-to-use supplementary food in a factorial design of interventions to evaluate strategies to reduce early mortality in adults and children starting ART.