TEMPORAL TRENDS IN GLOBAL PEDIATRIC COTRIMOXAZOLE USE AND IMPACT ON MORTALITY

Abstract number 840
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Background

- Cotrimoxazole (CTX) is recommended for all children recently diagnosed with HIV in order to prevent pneumocystis pneumonia
- Although CTX improves survival in HIV-infected children, the impact on mortality in children without severe immune deficiency is unclear
- We evaluated temporal trends in CTX use at antiretroviral therapy (ART) initiation and mortality rates while on CTX in the absence of severe immune deficiency

Methodology

- Pediatric IeDEA data collected between 1/Jan/2006 and 31/Mar/2016
- All 24 countries included considered low- or middle-income by World Bank criteria
- Severe immune deficiency defined by WHO 2006 age-specific CD4 thresholds
- Logistic regression to evaluate factors associated with using CTX at ART initiation
- Competing risk regression to assess factors associated with mortality on ART
  - Time-updated covariates: CTX use, severe immune deficiency, weight and anemia
  - Competing risk: Loss to follow-up
- Sensitivity analyses used multiple imputation to account for missing data

Results

- 54,113 children aged 1 month to 15 years were included
- Median age at ART initiation was 5.7 years and 51% were female
- **CTX use at ART initiation increased from 67% in 2006 to a peak of 86% in 2010 and then declined to 49% in 2015/16** (Figure 1)
- Higher proportions of CTX use at ART initiation were associated with severe immune deficiency, younger age, lower height-for-age z-score, anemia, starting ART between 2007-2012, and receiving care in East Africa (Table 1)
- **Among children without severe immune deficiency, the hazard of death did not differ with CTX use** (Table 2)
- Sensitivity analyses yielded similar results to the main analyses

Figure 1 – Trends in cotrimoxazole use and severe immune deficiency at ART initiation

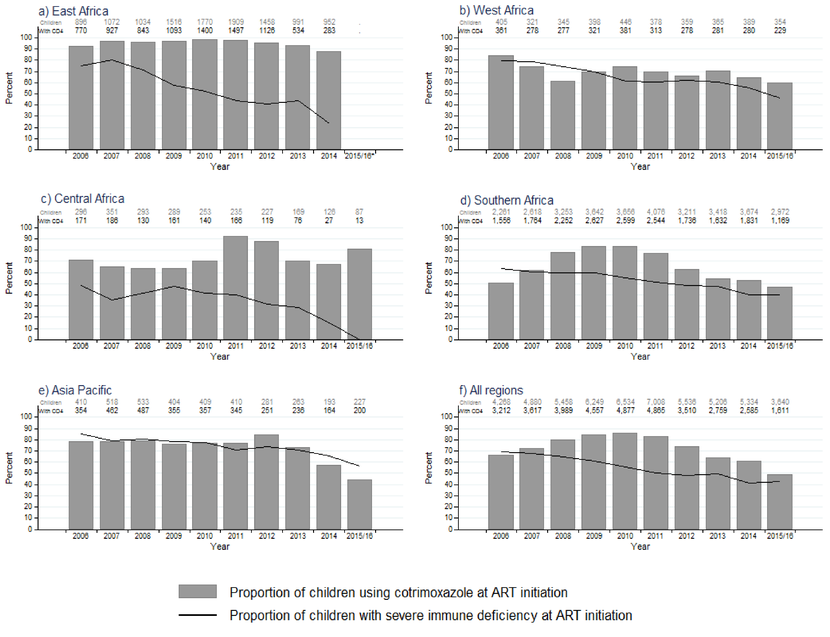


Table 1 – Factors associated with using CTX at ART initiation*

Characteristic	Children initiating ART	Children using CTX at ART initiation (%N)	Adjusted OR (95%CI)
Overall	54,113	39,811 (73·6)	
Age at ART initiation <1 year	4,688	3,460 (73·8)	1·18 (1·09, 1·28)
Age at ART initiation 1 to <5 years	19,702	14,657 (74·4)	1·00
Age at ART initiation 5 to <10 years	17,568	12,930 (73·6)	0·89 (0·85, 0·94)
Age at ART initiation ≥10 years	12,155	8,764 (72·1)	0·88 (0·83, 0·93)
Height-for-age z-score >-2·0	16,287	12,726 (78·1)	1·00
Height-for-age z-score -2·0 to -3·0	9,665	7,745 (80·1)	1·13 (1·06, 1·21)
Height-for-age z-score <-3·0	13,380	10,740 (80·3)	1·15 (1·08, 1·22)
Non-anemic	12,673	9,835 (77·6)	1·00
Anemic	14,849	11,737 (79·0)	1·08 (1·02, 1·15)
No severe immune deficiency	15,504	11,913 (76·8)	1·00
Severe immune deficiency	20,078	16,316 (81·3)	1·25 (1·18, 1·32)

*ART initiation year, geographic region and unknown groups were included in final model but data not shown; OR, odds ratio; CI, confidence interval

Table 2 – Factors associated with death on ART*

Characteristic	Deaths per 100 patient years (95%CI)	Adjusted sHR (95%CI)
Overall	1·85 (1·76, 1·94)	
Using CTX # No severe immune deficiency	0·62 (0·55, 0·71)	1·00
Not using CTX # No severe immune deficiency	0·37 (0·30, 0·45)	1·01 (0·77, 1·34)
Using CTX # Severe immune deficiency	6·18 (5·75, 6·65)	3·59 (3·06, 4·22)
Not using CTX # Severe immune deficiency	5·98 (5·24, 6·82)	6·76 (5·46, 8·38)
Age at ART initiation <1 year	3·46 (3·04, 3·94)	1·52 (1·29, 1·79)
Age at ART initiation 1 to <5 years	1·81 (1·66, 1·96)	1·00
Age at ART initiation 5 to <10 years	1·46 (1·33, 1·61)	0·85 (0·75, 0·97)
Age at ART initiation ≥10 years	1·96 (1·75, 2·20)	0·81 (0·70, 0·94)
Weight-for-age z-score >-2·0	0·58 (0·51, 0·65)	1·00
Weight-for-age z-score -2·0 to -3·0	1·25 (1·08, 1·44)	1·72 (1·43, 2·08)
Weight-for-age z-score <-3·0	5·72 (5·36, 6·10)	5·83 (5·07, 6·71)
Non-anemic	0·82 (0·74, 0·91)	1·00
Anemic	3·95 (3·66, 4·26)	1·73 (1·50, 2·00)

*ART initiation year, geographic region and unknown groups were included in final model but data not shown; CI, confidence interval; sHR, sub-distribution hazard ratio

Conclusion

Recent declines in pediatric CTX use coincide with declines in the proportion of children starting ART with severe immune deficiency. CTX did not improve survival among children without severe immune deficiency although use was not randomized and unmeasured confounders cannot be excluded.

Acknowledgements
The International Epidemiology Databases to Evaluate AIDS (IeDEA) is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, and the National Institute on Drug Abuse: Asia-Pacific, U01AI069907; CCASAnet, U01AI069923; Central Africa, U01AI096299; East Africa, U01AI069911; NA-ACCORD, U01AI069918; Southern Africa, U01AI069924; West Africa, U01AI069919. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.