

Improved Growth and Anemia in HIV-Infected African Children Taking Cotrimoxazole Prophylaxis

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The impact of cotrimoxazole (CTX) on growth and/or anemia was investigated in 541 human immunodeficiency virus-infected, antiretroviral therapy-naïve Zambian children enrolled in the Children with HIV Antibiotic Prophylaxis trial. Compared with children randomized to receive placebo, children randomized to receive CTX had slower decreases in weight-for-age ($P = .04$) and height-for-age ($P = .01$), and greater increase in hemoglobin level ($P = .01$). These findings argue for expanded early CTX use.

Cotrimoxazole (CTX) is an inexpensive, broad-spectrum antibiotic that reduces morbidity and mortality among human immunodeficiency virus (HIV)-infected children [1, 2] when taken daily as prophylaxis. CTX has activity against malaria and common bacterial pathogens causing diarrhea and pneumonia, even in areas of high resistance [1, 2]. In the Children with HIV Antibiotic Prophylaxis (CHAP) trial, the impact of CTX appeared to be principally attributable to reductions in lower respiratory tract infections [1, 2], with benefits across all ages and CD4 cell counts.

However, the precise mechanisms by which CTX reduces morbidity and mortality remain incompletely understood, and CTX may have activity beyond simply reducing intercurrent illnesses [3]. Because of the increasing appreciation of the benefits of CTX in HIV-infected individuals, we decided to further explore the impact of CTX on morbidity in the CHAP trial. In particular, malnutrition and anemia are common among HIV-infected children in Sub-Saharan Africa and are independently

associated with mortality [4]. We aimed to determine whether CTX prophylaxis has any effect on growth and anemia in HIV-infected African children.

METHODS

Our study was an observational analysis of children recruited to the CHAP trial. CHAP was a double-blind, randomized, placebo-controlled trial, conducted during 2001–2003, that enrolled HIV-infected Zambian children aged 1–14 years at University Teaching Hospital, Lusaka [1]. After informed consent was received from caregivers, children were randomized to receive daily CTX (240 mg for children <5 years of age; 480mg for children >5 years of age) or matching placebo. Antiretroviral therapy (ART) was not publicly available for children in Zambia during the trial; ART was received for <1% of child-time.

Children were followed up every month for the first 16 weeks, then every 2 months thereafter blood samples were obtained for full blood count, malarial film, and (from July 2001) CD4 cell count measurements. Weight and height were measured at all clinic visits and were expressed as weight-for-age Z score (WAZ) and height-for-age Z score (HAZ) [5]. The trial primary outcomes were mortality and adverse events possibly related to study drug. In October 2003, in accordance with advice from the Data and Safety Monitoring Committee, the trial was stopped prematurely because of substantial and sustained benefit in the CTX group [1].

Random effects models were used to estimate trends in WAZ, HAZ, CD4 cell percentage, and hematological parameters, using child-level random effects for baseline (intercept) and trend (slope) and fixed-effect slopes varying by randomized arm. For neutrophil count, a 2-slope model was fitted in the CTX group to estimate known early toxicity. A joint log-normal model for survival was used to adjust for informative censoring from death [6], which was higher in the placebo group. Analyses were undertaken using Stata, version 11.1 (Stata).

RESULTS

Five hundred forty-one children (median age, 4.4 years; interquartile range [IQR], 2.1–8.3 years) were enrolled; 268 were randomized to receive CTX and 273 to receive placebo. Half the children were male. Three-quarters (74%) had previously been hospitalized. Median follow-up time was 18.9 months (IQR, 13.6–24.0 months); 19.4 months (IQR, 14.7–24.1

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months) in the CTX group and 17.7 months (IQR, 12.9–23.9 months) in the placebo group. Overall, 74 children (28%) taking CTX, compared with 112 (42%) taking placebo, died ($P = .0002$) [1].

CD4 cell percentage measurements were available for 504 children (93% of cohort; median of 2 measurements per child). Mean CD4 cell percentage at baseline was 12.3% (standard deviation [SD], 7.0%). Mean annual change in CD4 cell percentage was +0.14% (95% confidence interval [CI], $-.55$ to $.83$) for the CTX group and -0.37% (95% CI, -1.18 to $.44$) for placebo (heterogeneity, $P = .33$); Table 1.

Weight and height measurements were available for all 541 children (median of 11 and 9 times per child in the CTX and placebo groups, respectively). There was high baseline prevalence of underweight and stunting, with mean WAZ and HAZ of -2.84 (SD, 1.63) and -3.25 (SD, 1.48), respectively. Subsequently, there was a statistically significant difference between children randomized to receive CTX or placebo in annual change in WAZ (mean, -0.15 [95% CI, $-.28$ to $-.03$] vs $-.35$ [95% CI, $-.49$ to $-.21$]; heterogeneity, $P = .04$) and HAZ (mean, -0.07 [95% CI, $-.15$ to $.01$] vs $-.22$ [95% CI, $-.30$ to $-.13$]; heterogeneity, $P = .01$). Taken together, children taking TMP-SMX had significantly slower decreases in WAZ and HAZ than did children taking placebo.

Hemoglobin level and platelet count measurements were available for 538 children (99% of cohort) and neutrophil counts for 537 children (99% of cohort), with a median of 5 measurements in both groups. Mean baseline hemoglobin level was 9.44 g/dL (SD, 1.27 g/dL); 49% of children had mild anemia (9–10.9 g/dL), 36% had moderate anemia (<9 g/dL), and 1% had severe anemia (<6 g/dL). Children taking CTX had a significantly greater subsequent annual increase in hemoglobin level than did children taking placebo (mean, $.33$ g/dL [95% CI, $.20$ – $.47$] vs $.08$ g/dL [95% CI, $-.08$ to $.24$]; heterogeneity, $P = .01$). Mean baseline neutrophil count was 3.21×10^9 cells/L (SD, 1.62

$\times 10^9$ cells/L), decreasing by a mean of $.50$ (95% CI, $-.74$ – $.26$) during the first 4 weeks in the TMP-SMX group only. Subsequently, neutrophil count increased similarly in children taking TMP-SMX and placebo (mean annual increase, $.47 \times 10^9$ cells/L [95% CI, $.25$ – $.69 \times 10^9$ cells/L] vs $.46 \times 10^9$ cells/L [95% CI, $.25$ – $.67 \times 10^9$ cells/L]; heterogeneity, $P = .97$). Mean baseline platelet count was 296×10^9 cells/L (SD, 116×10^9 cells/L); the annual decrease was similar in children taking CTX and placebo (mean, 13×10^9 cells/L [95% CI, 25 – 1×10^9 cells/L] vs 14×10^9 cells/L [95% CI, 28 – 1×10^9 cells/L]; heterogeneity, $P = .89$). Taken together, children taking CTX had a significantly greater increase in hemoglobin level but a greater initial decrease in neutrophil count; the decrease in platelet count was similar between groups.

DISCUSSION

The CHAP trial demonstrated that daily CTX prophylaxis reduces morbidity and mortality among HIV-infected children in Sub-Saharan Africa [1, 2]. Here, we present new data from this trial, showing that CTX use in untreated HIV-infected children is associated with slower decreases in weight- and height-for-age and improvements in anemia.

HIV-infected children in Sub-Saharan Africa are frequently underweight and stunted [4]. Because of the impact of nutritional status on mortality [4], improving weight is a critical goal of HIV programs. ART-naïve children taking CTX had at least a 2-fold reduction in weight-for-age decrease and 3-fold reduction in height-for-age decrease, compared with those taking placebo. We were unable to investigate the impact of CTX together with ART, because ART was not publicly available in Zambia during 2001–2003. Children in CHAP, therefore, had progressive deterioration in WAZ and HAZ because of ongoing HIV disease progression. However, future studies should investigate whether CTX and ART have an additive impact on growth.

Table 1. Baseline and Follow-up Growth and Hematological Parameters for Children Randomized to Receive Trimethoprim-Sulfamethoxazole (TMP-SMX) or Placebo

Variable	All Baseline value (mean, SD)	TMP-SMX group		Placebo group		P^a
		Weeks to last measurement (median, IQR)	Change per year (mean, 95% CI)	Weeks to last measurement (median, IQR)	Change per year (mean, 95% CI)	
CD4 cell percentage	12.3 (7.0)	50 (26, 80)	+ .14 ($-.55$, $+.83$)	41 (5, 71)	$-.37$ (-1.18 , $+.44$)	0.33
Weight-for-age Z score	-2.84 (1.63)	64 (34, 96)	$-.15$ ($-.28$, $-.03$)	48 (18, 74)	$-.35$ ($-.49$, $-.21$)	0.04
Height-for-age Z score	-3.25 (1.48)	64 (34, 96)	$-.07$ ($-.15$, $+.01$)	48 (18, 74)	$-.22$ ($-.30$, $-.13$)	0.01
Hemoglobin level, g/dL	9.44 (1.27)	51 (25, 91)	+ .33 ($+.20$, $+.47$)	47 (15, 72)	+ .08 ($-.08$, $+.24$)	0.01
Neutrophil count, $\times 10^9$ cells/L	3.21 (1.62)	51 (25, 91)	+ .47 ^b ($+.25$, $+.69$)	47 (15, 72)	+ .46 ($+.25$, $+.67$)	0.97
Platelet count, $\times 10^9$ cells/L	296 (116)	51 (25, 91)	-13 (-25 , -1)	47 (15, 72)	-14 (-28 , -1)	0.89

^a P value for difference in change per year between TMP-SMX and placebo groups.

^b After an initial 0.50 (95% CI, $.74$ – $.26$) decrease in neutrophil count during the first 4 weeks.

Growth impairment is multifactorial, relating to increased frequency of infections, poor oral intake, malabsorption, and persistent diarrhea [7]. The effects of CTX on growth may be primarily attributable to a reduction in severe intercurrent infections; reduced diarrhea among children receiving CTX is likely to be especially important. A trial in HIV-unscreened children admitted with measles in Guinea-Bissau found less pneumonia and significantly greater 1-month weight gain with 7 days of CTX, compared with placebo [8]. However, CTX could also theoretically lower immune activation in HIV-infected children. A major driver of immune activation is microbial translocation, whereby gut bacteria and microbial-associated products cross the intestinal mucosa to enter the systemic circulation [9]. CTX may lower intestinal bacterial burden and, thereby, reduce microbial translocation [3]. Microbial translocation is believed to underlie stunting malnutrition, even in HIV-uninfected children, through the growth-inhibiting effects of immune activation [10]. If future studies confirm that CTX impacts microbial translocation and/or immune activation, it might similarly improve growth in HIV-uninfected children. Unfortunately, stored plasma samples from CHAP were not available to investigate this further in HIV-infected children.

Anemia is common in HIV-infected children and is associated with poor prognosis [4]. In the present study, the vast majority of children had baseline anemia. However, children taking CTX had 4-fold greater increase in hemoglobin level than did those taking placebo. Anemia in HIV infection is multifactorial, but the most important mechanism is failure of erythropoiesis. CTX may plausibly reduce levels of cytokines that impair erythropoiesis [11], both directly, by reducing immune activation, and indirectly, by preventing infections. There was no clear impact of CTX on CD4 cell count decrease, consistent with findings from ART-treated adults in the Development of Antiretroviral Therapy in Africa trial [3]. However, children only had a median of 2 CD4 cell count measurements, and the finding of no difference between groups could alternatively reflect low power. Children taking CTX had a significant initial decrease in neutrophil count, likely because of toxicity. Subsequently, neutrophil counts increased at a similar rate in the placebo group, although the reason for the neutrophil count increase in both groups is unclear. One possible explanation is ongoing exposure and response to infections in both groups of ART-naïve children. Those receiving CTX had lower mortality but still had nonfatal infections driving the neutrophil response. Finally, CTX had no significant impact on platelet count, which decreased in both groups, reflecting ongoing untreated HIV infection.

There are several important implications from this study. CTX improves growth and anemia, even without ART; however, CTX roll-out in Sub-Saharan Africa remains poor. Although most countries have policies for CTX use, only 4% of eligible children

were receiving CTX in 2007 [12]; implementation is frequently impeded by lack of availability [13]. The current study argues for earlier identification of HIV-infected children and more widespread CTX use, to reduce morbidity and mortality and to improve growth and anemia, even where ART is unavailable. Where ART is available, TMP-SMX may have additive effects on nutrition and anemia. Because of the recent finding that TMP-SMX prophylaxis at ART initiation reduces mortality among HIV-infected adults [3], clinicians should strongly consider starting or continuing CTX therapy in children entering ART programs. Whether CTX can subsequently be stopped is being investigated in the Antiretroviral Research for Watoto trial, currently underway in Uganda and Zimbabwe.

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