The Impact of Daily Cotrimoxazole Prophylaxis and Antiretroviral Therapy on Mortality and Hospital Admissions in HIV-Infected Zambian Children

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Background. Data on the population effectiveness of cotrimoxazole prophylaxis and antiretroviral therapy (ART) in human immunodeficiency virus (HIV)–infected African children are few.

Methods. A total of 534 Zambian children with HIV infection were randomized to receive daily cotrimoxazole prophylaxis or placebo in the Children with HIV Antibiotic Prophylaxis trial. Following trial closure, children who received the placebo initiated cotrimoxazole prophylaxis, and all children were observed in a closed cohort. Mortality and hospital admission rates were compared, over calendar time, in 9-month periods: trial recruitment (March 2001 to April 2002, May 2002 to January 2003), trial follow-up to closure (February 2003 to October 2003), initial follow-up posttrial (November 2003 to July 2004), and early and later ART availability (August 2004 to April 2005, and May 2005 to May 2006, respectively).

Results. A total of 546 child-years of follow-up, 40 deaths, and 80 hospital admissions were observed between the time of trial closure and June 2006. A total of 117 of 283 children who were alive at trial closure received ART in the posttrial period (median child age at first use of ART, 8.8 years). Rates decreased in both groups during the trial period, suggesting a survivorship effect. Mortality and hospital admission rates before trial closure were 14 (95% confidence interval [CI], 9–21) deaths per 100 child-years and 24 (95% CI, 15–39) hospital admissions per 100 child-years, respectively, for children who were receiving cotrimoxazole, and were 23 (95% CI, 16–34) deaths per 100 child-years and 35 (95% CI, 23–53) hospital admissions per 100 child-years, respectively, for children who were receiving the placebo. After trial closure, rates remained stable in the cotrimoxazole group, but decreased to 15 (95% CI, 8–26) deaths per 100 child-years and 19 (95% CI, 10–41) hospital admissions per 100 child-years, respectively, for the group of children who received placebo and then initiated cotrimoxazole prophylaxis. In both groups combined, mortality rates decreased to 6 (95% CI, 3–11) deaths per 100 child-years and then 2 (95% CI, 0.8–6) deaths per 100 child-years during periods of ART availability; hospital admission rates decreased to 17 (95% CI, 11–27) hospital admissions per 100 child-years and 8 (95% CI, 4–15) hospital admissions per 100 child-years, respectively.

Conclusion. The benefits of once-daily cotrimoxazole prophylaxis continued throughout the trial and after trial closure. Mortality and hospital admissions decreased (by ~6-fold and ~3-fold, respectively) following ART availability, similar to findings observed in resource-rich countries.

The past 5 years have seen a major shift in the management of HIV infection in resource-limited countries with the introduction of cotrimoxazole prophylaxis and, more recently, antiretroviral therapy (ART). Two questions exist: whether benefits observed at the population level are similar to those observed in resource-rich countries and whether benefits observed in children in resource-limited countries match those observed in adults. Reductions in mortality of ~5-fold have been described following the introduction of 3- or 4-drug ART regimens in HIV-infected children in resource-rich countries, similar to observations made in adults [1, 2]. However, even in resource-rich countries, ART was introduced later for children because of difficulties developing appropriate formulations and the lack of age-specific pharmacokinetic data to guide pediatric dosing. In African countries, the issues of

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appropriate formulations for children are compounded by difficulties in drug transport, storage, and adherence for individual liquid formulations. The most readily available solid adult formulation (lamivudine-stavudine-nevirapine [Triomune; Cipla]) is also problematic, because it is not scored for splitting and must be cut to approximate the correct dose for children. It also contains a lower ratio of nevirapine to lamivudine and stavudine than is recommended for younger children [3]. In addition, late presentation to a health care facility, malnutrition, and the greater potential for immune reconstitution disease relating to high infectious disease burden may reduce the population-level impact of ART in children in resource-limited countries. However, comparisons with natural history survival (pre-ART) and with management of disease using cotrimoxazole prophylaxis alone have not been performed, because of few available data. Here, we describe changes over time in mortality and hospital admission rates during a 3-year period following introduction of daily cotrimoxazole prophylaxis and ART regimens to perinatally HIV-1–infected children who were originally enrolled in the Children with HIV Antibiotic Prophylaxis (CHAP) trial in Lusaka, Zambia.

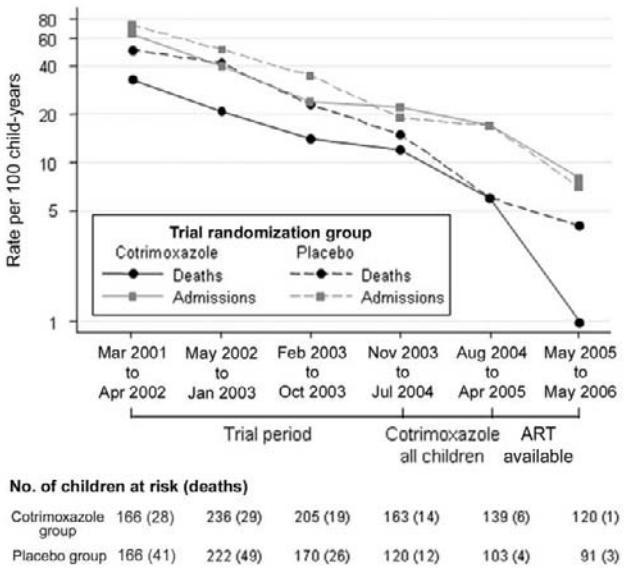

Figure 1. Mortality and hospital admissions rates by time period among 534 HIV-infected Zambian children randomized to receive either cotrimoxazole prophylaxis or placebo. ART, antiretroviral therapy.

METHODS

From March 2001 to January 2003, 534 HIV-infected Zambian children aged 1–14 years were randomized to receive daily cotrimoxazole prophylaxis or a placebo in the CHAP trial [4], following written consent from primary caregivers. The trial closed in October 2003, and children who were receiving placebo initiated cotrimoxazole prophylaxis. ART with lamivudine, stavudine, zidovudine, and nevirapine became available free-of-charge beginning August 2004, as individual liquid formulations (administered to the youngest children weighing <10 kg) and as parts of Triomune 30 tablets (nevirapine, 200 mg; lamivudine, 50 mg; and stavudine, 30 mg; administered to older children weighing >10 kg), according to World Health Organization (WHO) recommendations at the time [3, 5].

Mortality and hospital admission rates were compared across randomized groups over calendar time, censoring follow-up at death, loss to follow-up, or when the child stopped attending the clinic in analysis of hospital admission rates. Six 9–12-month periods were considered (figure 1): the first 2 periods covered trial recruitment (from March 2001 to April 2002 and from May 2002 to January 2003), the third period covered the time between the end of recruitment and trial closure (from February 2003 to October 2003), the fourth period covered the introduction of daily cotrimoxazole prophylaxis to all children, and the last 2 periods covered early and later ART availability (beginning August 2004 and May 2005, respectively). The division between these latter 2 periods was arbitrary, but they represent the period when only the children with the most severe illness initiated ART and a later period in which ART was made more widely available to all those who met WHO criteria. The cumulative probability of initiating ART was estimated by adjusting for death prior to starting treatment (competing risks). CD4 cell counts were expressed as a percentage of total lymphocyte counts (CD4 cell percentage). Weights were expressed as age-adjusted *z*-scores, with reference to uninfected children in the United Kingdom [6]. Number of child-years at risk for categories of weight-for-age score and CD4 cell percentage were estimated by time period using the last observation carried forward and censoring at death or at 8 weeks after the last observation (or at 24 weeks after the last observation for CD4 cell percentage). Time-averaged weight-for-age score and CD4 cell percentage were estimated per child for each time period and were compared between randomized groups using the Wilcoxon rank-sum test. Comparisons between periods 3 (last trial) and 6 (most-recent ART) were made for children who were initially randomized to receive cotrimoxazole by testing the observed median in period 6 against the estimated distribution of the median in period 3 (using the bootstrap method). Changes in individual weight-for-age score, CD4 cell count, and CD4 cell percentage were tested using the Wilcoxon matched-pairs signed-rank test, and changes according to pre-ART levels were compared using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Proportions were compared using Fisher's exact test. All analyses were performed using Stata software, version 8.2 (Statacorp).

The CHAP trial was approved by ethics committees at University Teaching Hospital (Lusaka, Zambia) and University College (London, United Kingdom). Ethics approval was granted

for continued visits every 8 weeks for all children in follow-up at the trial's closure.

RESULTS

At the trial's closure (October 2003), 674 child-years of observation had been accumulated for 534 children (265 of whom had been randomized to receive daily cotrimoxazole and 269 of whom had been randomized to receive placebo). A total of 76 children in the cotrimoxazole group and 116 children in the placebo group had died before trial closure. Characteristics of children in the last period of the trial (period 3) are shown in table 1.

Fifty-nine children (26 in the cotrimoxazole group and 33 in the placebo group) were lost to follow-up at or around trial closure, including 22 children who were lost to follow-up >3 months before trial closure. The children who were observed in the last 3 months of the trial but not subsequently (17 in the cotrimoxazole group and 20 in the placebo group) tended to be slightly younger (median age at trial closure, 5.7 years; interquartile range, 4.0–8.6 years) than those who continued to be observed (median age at trial closure, 6.6 years; interquartile range, 4.7–10.2 years; $P = .15$, by rank-sum test) and were somewhat more likely to be cared for by their mother at the time of trial closure (65% vs. 55% of children; $P = .30$) but did not differ by sex ($P = .86$). Between trial closure and June 2006, additional follow-up data on 163 children in the cotrimoxazole group and 120 in the placebo group were available, comprising a further 546 child-years of observation, 40 deaths, and 80 hospital admissions not ending in death. Between October 2003 and December 2003, 115 of 120 children who received the placebo initiated cotrimoxazole prophylaxis; 5 children were not attending the clinic, although follow-up information for them was available.

ART received. Overall, 127 children initiated ART: 34 did so before trial closure (most of whom were taking ART intermittently, according to ability to pay), 18 did so during early 2004, and 75 did so beginning August 2004, when combination ART became free of charge. The median age of the 93 children who initiated ART for the first time after trial closure was 8.8 years. The estimated cumulative probability of having initiated ART increased from 14% at the end of July 2004 to 27% by the end of April 2005 and 33% by the end of May 2006 for children who were randomized to receive cotrimoxazole. The corresponding increase observed in children who were initially receiving placebo was from 7% to 23% by the end of April 2005 and 26% by the end of May 2006; cumulative rates were lower, because a larger proportion of children had not survived and, therefore, could not initiate ART. Overall, the percentage of child-years at risk that were spent receiving ART was 0.5%, 0.8%, 1.6%, 5.9%, 31%, and 49% across the 6 periods.

Table 1. Characteristics of study population before trial closure and after widespread availability of antiretroviral therapy (ART).

Characteristic	Last trial period, Feb 2003–Oct 2003		Last period after widespread ART availability, May 2005–May 2006[a]
	Cotrimoxazole group	Placebo group	
Total no. of children at risk	205	170	211
Age at start of period, median years (IQR)	5.4 (3.5–8.8)	5.9 (4.1–9.5)	7.9 (6.0–11.7)
No. of children who ever used ART[b]	19	6	107
Percentage of child-years receiving ART (total child-years)	2.0 (141)	1.1 (112)	49 (184)
Weight-for-age score, median (IQR)[c]	−2.3 (−3.3 to −1.4)	−2.8 (−3.5 to −1.6)	−2.0 (−3.1 to −1.2)
Percentage of child-years, by weight-for-age score (total child-years)			
Less than −3	30 (132)	37 (99)	23 (179)
Greater than or equal to −3	70 (132)	63 (99)	77 (179)
CD4 cell percentage, median value (IQR)[d]	13 (8–18)	13 (7–17)	19 (13–27)
Percentage of child-years, by CD4 cell percentage (total child-years)			
<5%	9 (128)	16 (97)	4 (163)
5%–14%	51 (128)	41 (97)	34 (163)
⩾15%	40 (128)	43 (97)	62 (163)

NOTE. IQR, interquartile range

[a] Data are for cotrimoxazole and placebo groups combined.

[b] ART use was intermittent, according to ability to pay, during the trial period and was continuous when started during the last 2 periods.

[c] Time-averaged value computed per child for each interval. Data are for 186 children in the cotrimoxazole group and 146 children in the placebo group for the last trial period, and 195 children for the last period after widespread ART availability. $P = .04$ for the difference between randomization groups in the last trial period and $P = .09$ for the difference in the cotrimoxazole group between the last trial period and the last period after widespread ART availability .

[d] Time-averaged value computed per child for each interval. Data are for 177 children in the cotrimoxazole group and 129 children in the placebo group for the last trial period, and 180 children for the last period after widespread ART availability. $P = .82$ for the difference between randomization groups in the last trial period and $P < .001$ for the difference in the cotrimoxazole group between the last trial period and the last period after widespread ART availability.

Mortality and hospital admission rates over calendar time. Mortality and hospital admission rates decreased in both groups during the trial period, suggesting a survivorship effect (figure 1)—namely, that the sickest children, who were also recruited earliest in the trial, died more rapidly, leaving "healthier survivors" at risk. The benefits of cotrimoxazole prophylaxis were evident throughout the trial ($P < .001$ and $P = .13$ for difference in mortality and hospital admission rates, respectively, across 3 trial periods). Rates during the 9 months prior to trial closure were 14 (95% CI, 9–21) deaths per 100 child-years and 24 (95% CI, 15–39) hospital admissions per 100 child-years in the cotrimoxazole group versus 23 (95% CI, 16–34) deaths per 100 child-years and 35 (95% CI, 23–53) hospital admissions per 100 child-years in the placebo group. In the 9 months following trial closure, mortality and hospital admission rates decreased among the group that was randomized to receive placebo and who subsequently initiated cotrimoxazole, to 15 (95% CI, 8–26) deaths per 100 child-years and 19 (95% CI, 10–41) hospital admissions per 100 child-years, similar to the rates observed in the cotrimoxazole group in the last trial period. In contrast, rates remained stable in children who were randomized to receive cotrimoxazole. In both groups combined, mortality rates decreased significantly, from 13 (95% CI, 9–20) deaths per 100 child-years in the period following trial closure to 6 (95% CI, 3–11) deaths per 100 child-years (incidence rate ratio [IRR], 0.45 [95% CI, 0.22–0.93]; $P = .03$) and to 2 (95% CI, 0.8–6) deaths per 100 child-years (IRR, 0.16 [95% CI, 0.06–0.47]; $P = .001$) during the periods of ART availability. Hospital admission rates decreased from 21 (95% CI, 14–31) hospital admissions per 100 child-years to 17 (95% CI, 11–27) hospital admissions per 100 child-years (IRR, 0.82 [95% CI, 0.49–1.40]; $P = .48$) and 8 (95% CI, 4–15) hospital admissions per 100 child-years (IRR, 0.37 [95% CI, 0.19–0.75]; $P = .005$) during the 2 periods of ART availability.

Impact of weight-for-age score and CD4 cell percentage. During the trial, mortality rates were highest among children who had the lowest current weight-for-age score. Across the 3 posttrial periods combined, rates were 15 (95% CI, 10–24) deaths per 100 child-years in children with weight-for-age scores less than −3 and 3 (95% CI, 2–6) deaths per 100 child-years in children with weight-for-age scores greater than or equal to −3 (IRR, 5.25 [95% CI, 2.50–11.01], similar to the IRR observed during the trial period [data not shown]). As expected, mortality was also greater, to a similar extent, among children who had a low current CD4 cell percentage during the trial period (data not shown) and after the trial, where mortality rates were 7 (95% CI, 5–12) deaths per 100 child-years among children with a CD4 cell percentage <15%, compared with 2 (95% CI, 0.7–7) deaths per 100 child-years among those with a CD4 cell percentage ⩾15% (IRR, 4.03 [95% CI, 1.38–11.80]).

Population weight-for-age scores increased during the trial in both groups, consistent with a survivorship effect and early recruitment of very malnourished children, with a trend towards higher scores in the cotrimoxazole group ($P = .05$, $P = .01$, and $P = .04$ in periods 1–3, respectively; data from period 3 are presented in table 1). CD4 cell percentage was measured infrequently (at 0, 4, 12, and 24 weeks and every 24 weeks thereafter) but population CD4 cell percentage values appeared to be similar among the 2 groups during the trial period ($P = .26$, $P = .59$, and $P = .82$ in periods 1–3, respectively; data from period 3 are presented in table 1) and changed little with time during the trial. Population CD4 cell percentage values and, to a lesser extent, population weight-for-age scores increased in the periods after the trial, when ART became freely available (table 1).

Individual response to ART. On an individual-child basis, among the 76 children who started ART after October 2003 for whom values were available from before and 6 months after ART initiation (median child age, 8.1 years), median (IQR) weight-for-age score before ART was initiated was −2.4 (−3.4 to −1.6; median weight, 20 kg). Median CD4 cell percentage and absolute CD4 cell count were 6% (IQR, 3%–9%; 24 of 66 children had a CD4 cell percentage <5%) and 218 cells/mm^3 (IQR, 76–374 cells/mm^3; 19 of 64 children had an absolute CD4 cell count <100 cells/mm^3), respectively. At 6 months, weight-for-age score had increased significantly by a median of 0.21 (IQR, −0.09 to 0.54; $P = .004$; median increase, 1.8 kg), with the greatest increases observed in children who had had the lowest pre-ART weight-for-age scores (median increases were 0.40, 0.15, and 0.08 in children whose pre-ART weight-for-age scores were less than −3, −3 to −2, and greater than or equal to −2, respectively; $P = .02$). CD4 cell percentage and CD4 cell count also increased significantly by a median of 12% (IQR, 7%–18%; $P < .001$) and 272 cells/mm^3 (IQR, 148–406 cells/mm^3; $P < .001$), respectively. Increases in CD4 cell percentage were smaller among children whose pre-ART CD4 cell percentage was <5% (median increase, 9%; IQR, 6%–13%) compared with children whose pre-ART CD4 cell percentage was 5%–9% (median increase, 13%; IQR, 9%–20%) and ⩾10% (median increase, 16%; IQR, 9%–22%) ($P = .01$ for CD4 cell percentage <5% vs. ⩾5%). Increases in CD4 cell count were smaller in children whose pre-ART absolute CD4 cell count was <100 cells/mm^3 (median increase, 152 cells/mm^3; IQR, 81–217 cells/mm^3) than in children whose pre-ART absolute cell count was ⩾100 cells/mm^3 (median increase, 317 cells/mm^3; IQR, 218–588 cells/mm^3; $P < .001$).

Fourteen children died during the periods of ART availability. Causes of death for the 6 children who had received ART were HIV encephalopathy (in 1 child who had received 5 months of ART), tuberculosis (in 1 child who had received 5 months of ART), pneumonia (in 2 children who had received <1 month

of ART and 25 months of intermittent ART, respectively), diarrhea (in 1 child who had received <1 month of ART), and cerebrovascular accident (in 1 child who had received 3 months of ART). Eight children died before initiating ART (all deaths were due to HIV-related causes). Malnutrition was considered to be an important contributor to mortality; 9 of the 14 children who died had a weight-for-age score less than −3, including all 6 of the children who died while receiving ART. Similarly, low CD4 cell percentage was also a contributor to mortality; 6 of the 14 children who died (3 of the 6 who had received ART and 3 of the 8 who had not) had a CD4 cell percentage <5%.

There were 41 hospital admissions involving 30 children during ART periods 5 and 6 (340 child-years of follow-up): 23 hospital admissions involved children who were receiving ART (8 of the 23 admissions involved children who had received <3 months of ART), and 18 were for children who had not yet initiated ART. For 19 hospital admissions (46%), at least 2 diagnoses were reported. As in the pre-ART periods 1–4 (813 child-years of observation), most diagnoses made during periods 5 and 6 were of presumptive respiratory conditions: pneumonia or bronchiectasis (27 hospital admissions), tuberculosis (15 hospital admissions), and nonsevere respiratory infections (6 hospital admissions), with pneumonia and tuberculosis often reported together [7]. In comparison with hospital admissions during periods 1–4, there were decreases observed in the proportion of hospital admissions due to malnutrition (0 of 41 hospital admissions in periods 5 and 6 vs. 34 [11%] of 318 hospital admissions in periods 1–4) and diarrhea or dehydration (1 [2%] of 41 hospital admissions vs. 50 [16%] of 318 hospital admissions).

DISCUSSION

Long-term follow-up of the cohort of children who were originally recruited into the CHAP trial provides an overview of mortality and hospital admission rates among poor African HIV-infected children (median age at recruitment, 4.4 years) over 5 calendar years that encompass eras of no treatment, daily cotrimoxazole prophylaxis, and receipt of ART. Although mortality was decreasing in this aging cohort during the trial (most likely because of survivorship bias), there was a sustained benefit observed with cotrimoxazole therapy over placebo. After the trial, mortality decreased in the placebo group when these children initiated cotrimoxazole prophylaxis, until it matched rates observed in those who were originally randomized to receive cotrimoxazole. Mortality and hospital admissions decreased even further (by 6- and 3-fold, respectively) in the periods of increasing ART availability, similar to the impact of ART observed in children in resource-rich countries [1, 2].

Few studies have collected data on the natural history of HIV infection in African children postinfancy prior to the introduction of ART. Those data that are available are often incomplete because of selective loss to follow-up (Duong T, personal communication) or have focused on the follow-up of young children who were originally enrolled in studies of the prevention of mother-to-child transmission of HIV infection with very high rates of mortality [8]. The CHAP trial provided information on the natural history of HIV infection in older children [9], data that are relevant to the current situation in many African countries where HIV infection is first diagnosed at older ages when children present with symptoms to medical facilities. Our data demonstrate a continued benefit from cotrimoxazole prophylaxis in such children while they are waiting to initiate ART. When ART became available to this cohort, we found that, similar to the many recent reports from African programs involving children initiating ART [10, 11], most deaths that occured while children were receiving ART occurred early after initiation of ART and in children who had the most marked immunosuppression. Children in the CHAP study were among the first in Zambia to receive ART from the government totally free of charge after the end of the trial. However, there is no doubt that, in ideal circumstances, many of these children would have initiated ART earlier in the course of their disease; therefore, ART impact in resource-limited areas may increase as programs mature and children are able to initiate ART earlier. However, we also found that malnutrition was a very important contributor to mortality, highlighting the importance of nutrition in children with HIV infection who are waiting to enroll in ART programs, whether malnutrition is related to the underlying HIV disease or to social circumstances. Further research on the management of ART, including timing of initiation in HIV-infected children from areas with high background rates of malnutrition, is required.

We collected detailed data on hospital admissions throughout the trial [7], as well as data on hospital admissions in the ART era. The 3-fold decrease that was observed in hospital admission rates following ART availability in the CHAP study is somewhat less than the 5-fold decreases reported in a pediatric cohort in the United Kingdom and Ireland (the Collaborative HIV Paediatric Study [CHIPS] [1]), but, in both studies, reductions in hospital admissions rates occurred slightly later than reductions in mortality rates. Because many pediatric wards in African hospitals are overburdened with HIV-infected children, this reduction in hospital admissions may have important cost implications. We are undertaking a detailed cost-effectiveness analysis of cotrimoxazole prophylaxis, to be followed by an analysis of the cost-effectiveness of ART in children. Cost data collected from this study, which was embedded in the public pediatric service at University Teaching Hospital, should provide important information for decision makers about treatment and management strategies for African children in the era of HAART.

During the CHAP trial itself, there was some support for improved population weight-for-age scores in the cotrimoxa-

zole group, compared with the placebo group; in contrast, population CD4 cell percentage was similar among the 2 groups. Higher weight-for-age score may partly explain the survival benefits in the cotrimoxazole group [7]. Population and individual weight-for-age scores and CD4 cell percentage increased as ART became available. Median short-term increases in CD4 cell percentage of 12% in children initiating ART are similar to increases seen in resource-rich countries [12–14]. However, in contrast to the CHIPS cohort, in which increases in CD4 cell percentage were greatest in children who had the lowest pre-ART CD4 cell percentages [13], we observed smaller CD4 cell percentage increases in those children who had very low pre-ART CD4 cell percentages. This may, in part, reflect the older child age at ART initiation in our study (median age, 8.1 years in our cohort vs. 4.2 years in the CHIPS cohort), but it may also be a result of the degree of malnutrition these children experienced. Resino et al. [14] also reported slower increases in CD4 cell percentage among children (median age, ~7 years) who were initiating combination ART with a CD4 cell percentage value <5%; however, numbers of children were small, and all children in this observational study had received prior single or dual nucleoside reverse-transcriptase inhibitor therapy. More information and, in particular, meta-analysis, may help to clarify which children may be disadvantaged by initiating ART with very advanced immunosuppression.

We have used an analysis of population effectiveness [15] to investigate the impact of cotrimoxazole prophylaxis and ART on mortality and hospital admissions. Such analysis divides calendar time at risk into periods with different clinical management strategies and then compares survival among these periods to assess the impact of the different strategies. A major bias in directly comparing children who are initiating ART or cotrimoxazole prophylaxis with those who are not is "confounding by indication" [16], which can be avoided by analysis of population effectiveness. Decisions to start therapy are influenced by both prognostic and external factors, and confounding by indication can occur if children starting ART or cotrimoxazole prophylaxis differ from those who are not by ≥ 1 unmeasured factors that are also predictors of response. Nevertheless, it is possible that improvements in clinical care other than the introduction of cotrimoxazole prophylaxis and ART could be partly responsible for the decreases in mortality and hospital admissions that we observed. An obvious limitation in using a closed cohort for the analysis of effectiveness of therapy in a population is the inherent assumption that comparisons within the cohort can be made across different time periods. Given the age of these HIV-infected children, in the absence of ART, mortality and hospital admissions rates would be expected to remain reasonably constant (or even increase) when the cohort was closed, as was observed initially in the cotrimoxazole group. We were able to use the original randomization to demonstrate that the introduction of cotrimoxazole prophylaxis to the placebo group was associated with a reduction in mortality. Loss to follow-up was low; however, if it had been nonrandom, it could have affected our estimated rates.

In summary, introduction of ART is associated with decreases in mortality and hospital admissions rates among HIV-infected children that are similar to corresponding decreases observed in resource-rich countries. Daily cotrimoxazole prophylaxis has been shown to substantially reduce non–*Pneumocystis jiroveci*–related deaths and hospital admissions in children after infancy, and it is a recommended standard of care for all HIV-infected children [17]. Its added impact among children who are receiving ART requires further study. Given that most HIV-infected children currently initiating ART in Africa are older survivors, the potential for impaired immune response in those who are initiating ART with very low CD4 cell counts requires further investigation with larger cohorts over a longer period of follow-up. Findings may have an impact on the recommended timing of ART initiation in African children, also bearing in mind the challenge of managing severe malnutrition in HIV-infected children, a key independent predictor of survival [9].

STUDY INVESTIGATORS

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