Clinical Outcomes and CD4 Cell Response in Children Receiving Antiretroviral Therapy at Primary Health Care Facilities in Zambia

Carolyn Bolton-Moore, MBChB
Mwangelwa Mubiana-Mbewe, MBChB
Ronald A. Cantrell, MPH
Namwinya Chintu, MBChB
Elizabeth H. Chi, MD
Moses Sinkala, MBChB, MPH
Chipepo Kankasa, MBBS
Craig M. Wilson, MD
Catherine M. Wilfert, MD
Alfred Mwango, MBChB
Jens Levy, PhD
Elaine J. Abrams, MD
Marc Bulterys, MD, PhD
Jeffrey S. A. Stringer, MD

By the end of 2006, an estimated 2.3 million children worldwide were living with human immunodeficiency virus type 1 (HIV-1). Although most children acquire the virus through largely preventable mother-to-child transmission, roll-out of perinatal HIV prevention services has been sluggish worldwide. As a result, each day more than 1000 children become newly infected. Without treatment, approximately half will die by their second birthday; however, lives can be extended and morbidity avoided with combination antiretroviral therapy (ART).

In Zambia, recent progress has been made toward reducing new pediatric infections through aggressive scale-up of perinatal HIV prevention services. Despite these efforts, 130 000 children are

Context The Zambian Ministry of Health provides pediatric antiretroviral therapy (ART) at primary care clinics in Lusaka, where, despite scale-up of perinatal prevention efforts, many children are already infected with the human immunodeficiency virus (HIV).

Objective To report early clinical and immunologic outcomes of children enrolled in the pediatric treatment program.

Design, Setting, and Patients Open cohort assessment using routinely collected clinical and outcome data from an electronic medical record system in use at 18 government primary health facilities in Lusaka, Zambia. Care was provided primarily by nurses and clinical officers (“physician extenders” akin to physician assistants in the United States). Patients were children (<16 years of age) presenting for HIV care between May 1, 2004, and June 29, 2007.

Intervention Three-drug ART (zidovudine or stavudine plus lamivudine plus nevirapine or efavirenz) for children who met national treatment criteria.

Main Outcome Measures Survival, weight gain, CD4 cell count, and hemoglobin response.

Results After enrollment of 4975 children into HIV care, 2938 (59.1%) started ART. Of those initiating ART, the median age was 81 months (interquartile range, 36-125), 1531 (52.1%) were female, and 2087 (72.4%) with World Health Organization stage information were in stage III or IV. At the time of analysis, 158 children (5.4%) had withdrawn from care and 382 (13.0%) were at least 30 days late for follow-up. Of the remaining 2398 children receiving ART, 198 (8.3%) died over 3018 child-years of follow-up (mortality rate, 6.6 deaths per 100 child-years; 95% confidence interval [CI], 5.7-7.5); of these deaths, 112 (56.6%) occurred within 90 days of therapy initiation (early mortality rate, 17.4/100 child-years; post–90-day mortality rate, 2.9/100 child-years). Mortality was associated with CD4 cell depletion, lower weight-for-age, younger age, and anemia in multivariate analysis. The mean CD4 cell percentage at ART initiation among the 1561 children who had at least 1 repeat measurement was 12.9% (95% CI, 12.5%-13.3%) and increased to 23.7% (95% CI, 23.1%-24.3%) at 6 months, 27.0% (95% CI, 26.3%-27.6%) at 12 months, 28.0% (95% CI, 27.2%-28.8%) at 18 months, and 28.4% (95% CI, 27.4%-29.4%) at 24 months.

Conclusions Care provided by clinicians such as nurses and clinical officers can result in good outcomes for HIV-infected children in primary health care settings in sub-Saharan Africa. Mortality during the first 90 days of therapy is high, pointing to a need for earlier intervention.

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believed to be already infected, and 25,000 to 30,000 are in urgent need of ART. During May of 2004, with financial resources from the US President’s Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis and Malaria, and other sources, the Zambian Ministry of Health initiated an ART program at primary care sites within the Lusaka Urban Health District. A stated priority of this program has been the inclusion of children. This report describes our early clinical experience treating HIV-infected children in primary health clinics where pediatric specialty expertise is generally not available.

METHODS

The pediatric treatment program began in May 2004 and operates in 18 of the Lusaka District’s 27 primary care facilities. Physicians are scarce—the entire district shares a single physician—but the nearby University Teaching Hospital is well staffed and acts as a referral and training center. We therefore developed pediatric-specific clinical care protocols and training plans that focus on nonphysician clinicians (nurses and clinical officers).

Clinical officers provided the preponderance of care to children in this cohort. Clinical officers are “physician extenders” akin to physician assistants in the United States. They have 3 years of training beyond grade 12. Their training is clinical and practical and is focused on the primary care of adults and children. In Zambia, clinical officers are allowed to prescribe most medications (excluding narcotics and other controlled substances). As a health care workforce cadre, they are critical in the region because they can be trained relatively quickly (physicians require a minimum of 7 years), and their degrees are not generally portable; ie, they are less likely than physicians and nurses to emigrate to areas having better working conditions in more affluent countries. The use of clinical officers and nurses to provide ART in primary care settings is an example of “task shifting,” a concept that has become increasingly important to policy makers who seek to further extend the reach of HIV services in the face of a severe human resources crisis. In February 2007, the World Health Organization (WHO) and Office of the Global AIDS Coordinator (part of PEPFAR) convened a meeting to discuss task shifting, in which the idea was endorsed and a call was issued for careful evaluation of its effectiveness and acceptability.

Children are referred to the program primarily from the outpatient department or maternal-child health clinics, although referrals from other sites and services do occur. We require documented seropositivity for enrollment. Children younger than 18 months may enroll with confirmation of positive maternal HIV serostatus.

The initial assessment includes a pediatric history and physical examination as well as determination of clinical disease stage by WHO criteria. Hematology, chemistry, and CD4 cell studies (absolute count and percentage of lymphocytes) are performed at baseline and monitored every 6 months or when clinically indicated. We were not able to distinguish between scheduled and clinically indicated CD4 cell measurements in this analysis, but the exact number of values is indicated herein. Our flow cytometers report both absolute CD4 cell count and CD4 cell percentage of lymphocytes on a given sample. However, WHO and also Zambian national guidelines advise that clinicians use CD4 cell percentage for assessment of children younger than 60 months and absolute CD4 cell count for children 60 months or older.

In accordance with new WHO guidelines, we modified our staging criteria and ART eligibility criteria in August 2006. This raised threshold CD4 cell percentage levels for severe immunodeficiency to less than 25% for infants 11 months or younger, less than 20% for children aged 12 to 35 months, and less than 15% for children 3 years or older. Children in this report thus started ART based on the guidelines that were operant at the time of enrollment. Because virologic testing has only recently become available in public-sector clinics, HIV-exposed children younger than 18 months who meet clinical criteria, immunologic criteria, or both were treated presumptively, as recommended by the WHO (ie, HIV-1 antibody–positive, plus clinical signs of advanced immunosuppression).

After treatment initiation, patients are seen weekly for the first 4 weeks and then monthly. At each visit, a nurse or pharmacy technician performs an adherence assessment using 3-day pill recall and open-ended questioning. Those who need additional counseling, education, or assistance receive it, including an option of home visits by community health workers. These adherence counseling sessions are also used to provide support and education regarding drug adverse effects and toxicities. Specific reasons for regimen changes are not captured in our electronic database. Clinicians undergo initial and ongoing training in recognition and management of drug toxicities. Protocols are in place to manage suspected toxicities. Other than a drug stockout, which has not happened in our pediatric drug supply, there are no other reasons for single-drug substitutions. Thus, we can reasonably assume that any such regimen change is made on the basis of drug intolerance or toxicity.

Weight-for-age is plotted against WHO growth charts for children younger than 5 years and against US Centers for Disease Control and Prevention charts for children 5 years or older, because WHO charts are not available for older children. All exposed infants are prescribed cotrimoxazole prophylaxis from 6 weeks of age. Older children are prescribed cotrimoxazole at the initial visit but continue the drug at subsequent visits only if ART eligibility criteria are met. Cotrimoxazole is discontinued once CD4 cell counts are maintained above threshold levels (the same agespecific levels as are used for treatment
eligibility\textsuperscript{11,12} for 6 months while receiving ART. Children whose history and clinical picture are suggestive of tuberculosis infection receive chest radiographs and, when possible, provide sputa for detection of acid-fast bacilli. We use empirical antibiotics to rule out bacterial pneumonia prior to starting antituberculosis therapy. Gastric lavage and skin testing for tuberculosis are not generally available.

First-line drugs include zidovudine or stavudine plus lamivudine plus nevirapine or efavirenz. Where possible, children with hemoglobin levels less than 10 g/dL are not prescribed zidovudine. According to Zambian national guidelines,\textsuperscript{13} nevirapine is used preferentially in all children, while efavirenz is reserved for those requiring concurrent treatment with rifampicin or not tolerating nevirapine.

**Appointment and Adherence Tracking**

Patient data are recorded using a locally developed electronic medical record system called “Smart Care.”\textsuperscript{17} Following patient encounters, an on-site data clerk enters designated elements from clinical forms into the database. This system allows tracking of program performance indicators, tabulation of pharmacy dispensation data, and generation of lists of patients who miss clinic appointments and require follow-up at home.

Adherence to therapy is assessed via timeliness of ART drug collection.\textsuperscript{18-20} Actual pharmacy visit dates are compared with scheduled appointment dates for each patient, and the cumulative number of days late a patient has been during the course of his or her time receiving ART is determined. Standardization of this variable is accomplished by dividing it by the total number of months of therapy. Children receiving ART and more than 10 days late for a scheduled appointment are followed up by community health workers at their homes. Children who do not receiving ART are not followed up until they are at least 10 days late. Children who are at least 30 days late for a clinical or pharmacy appointment and not known to have died or formally withdrawn from the program are considered “late” in this analysis. We use the term “active” to describe children who are neither late for follow-up nor formally withdrawn from the program.

**Laboratory Studies**

The CD4 cell assessment (absolute count and percentage of lymphocytes) is conducted at a central laboratory using a Beckman Coulter Epics XL-MCL 4-color flow cytometer (Beckman Coulter Inc, Miami, Florida). Baseline levels of aspartate aminotransferase, alanine aminotransferase, and creatinine are measured with the Roche COBAS Integra 400 Plus (Roche Diagnostics, Basel, Switzerland). Complete blood cell counts are performed centrally using the Sysmex XT2000i analyzer (Sysmex America Inc, Mundelein, Illinois). Some district facilities also perform hemoglobin testing locally with a field photometer assay (HemoCue AB, Helsingborg, Sweden). The HIV antibody testing performed in the Lusaka District involves a screening rapid test (Determine HIV1/2; Abbott Laboratories, Abbott Park, Illinois), with positive results confirmed using a second rapid test (Uni-Gold; Trinity Biotech, Wicklow, Ireland). For diagnosis of HIV infection in infants, we used the polymerase chain reaction to detect HIV-1 proviral DNA on dried filter paper specimens (Roche Amplicor HIV-1 DNA Monitor v. 1.5; Roche Molecular Systems, Branchburg, New Jersey).

**Statistical Analyses**

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the Pearson $\chi^2$ test statistic. Kaplan-Meier curves were fit to assess survival functions stratified by CD4 cell value (absolute count and percentage of lymphocytes), WHO stage, weight-for-age $z$ (WAZ) score, and hemoglobin concentration at initiation of therapy, and the log-rank test was used to assess statistical difference among groups. Hazard ratios (HRs) for mortality were estimated using Cox proportional hazards regression,\textsuperscript{21} and the proportional hazards assumption was tested for all covariates using the Kolmogorov-type supremum test.\textsuperscript{22} Model assumptions were met for all reported analyses.

For children receiving ART, we calculated mortality rates overall, at 90 days of therapy, and after 90 days of therapy with exact 95% confidence limits. These time thresholds are consistent with prior published conventions.\textsuperscript{8,22} Reported overall mortality rates consider active patients only; ie, they exclude those children who are late or withdrawn from the program. Some children ($n=513$) were initially ineligible for ART but became eligible and started ART at a subsequent visit. For the purposes of analysis, we consider only the post-ART outcomes in this group of children and consider their “baseline” measurements (eg, WAZ score, CD4 cell percentage) to be those taken at the time of ART initiation.

For the mortality analyses, we generated separate proportional hazards regression models for all children, those younger than 18 months, those aged 18 to 59 months, and those 60 months or older. This was done to mimic age cutoffs for treatment eligibility and available weight-for-age reference standards. Factors found in univariate analysis to be significant at the $P<.10$ level, as well as those found significant in our prior analysis of adults in the same setting,\textsuperscript{8} were included in multivariate proportional hazards regression models.

In crude and adjusted models that included all children, we used CD4 cell percentage (rather than absolute count) because it is known to be stable across all age categories.\textsuperscript{11} In June 2005, the WHO modified its 3-stage model to one with 4 distinct stages, and this was adopted in Zambia.\textsuperscript{23} To accommodate these changes, WHO stages III and IV are grouped together in our analyses. Only those children with complete covariate and outcomes data are considered in the multivariate models.
children (31.2%) never started ART.

To assess whether there were survival differences based on use of zidovudine vs stavudine, we categorized drug exposure (stavudine vs zidovudine) in the Cox models by intention-to-treat, in which a given child’s drug exposure was determined by his or her first-month dispensation. We dichotomized hemoglobin concentration at 8.0 g/dL and adherence at the 90th percentile based on prior convention.8 All reported P values are 2-sided, and P < .05 was used to determine statistical significance except where otherwise indicated. Data were analyzed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). On July 2, 2007, the data set was locked for analysis and analyses were performed between that date and July 28, 2007. We requested and were granted blanket exemption for this programmatic analysis, which was approved under expedited human subjects review by the research ethics committee of the University of Zambia and by the institutional review boards of the US Centers for Disease Control and Prevention and the University of Alabama at Birmingham.

RESULTS

Between May 1, 2004, and June 29, 2007, 4975 HIV-1 infected children (<16 years of age) were evaluated in the primary health care clinics in Lusaka (FIGURE 1). Of these, 659 (13.2%) did not return for a subsequent ART eligibility visit, and 46 (0.92%) were already receiving ART at enrollment and are thus not given further consideration in this analysis. Of the 4270 treatment-naive patients who returned for an ART eligibility visit, 2938 (68.8%) started ART and contributed a median of 378 days of follow-up to the analysis (interquartile range [IQR], 138 to 692 days). This group includes 2425 children who started ART immediately as well as 513 children who started ART after undergoing follow-up for at least 90 days in the program (Figure 1). A total of 1332 children (31.2%) never started ART.

As of July 2, 2007, 2200 children (74.9%) who had started ART were alive and active in the program, 198 (6.7%) were documented as dead, 158 (5.4%) had withdrawn, and 382 (13.0%) were late for follow-up (see “Methods”). Of children who did not start ART, 541 (40.6%) were alive and active in the program, 85 (6.4%) were documented as dead, 85 (6.4%) had withdrawn, and 621 (46.6%) were late for follow-up.

Cohort Characteristics

The median age at presentation of the 4270 children who enrolled into care was 65 (IQR, 23 to 114) months, with 811 children (19.0%) younger than 18 months, 1202 (28.1%) aged 18 to 59 months, and 2257 (52.9%) 60 months or older (TABLE 1). There were 2136 female children (50.0%), and 243 children (5.7%) had active tuberculosis documented at presentation. The median hemoglobin concentration among the 3435 children (80.4%) with baseline values was 10.2 (IQR, 8.9 to 11.4) g/dL. Baseline weights were available for 3909 children (91.5%). Approximately half of the children were more than 2 standard deviations below the mean expected weight for their age (median WAZ score, −2.0; IQR, −3.2 to −0.9). Stratification by age revealed similar WAZ score distributions for all children, irrespective of age (Table 1, upper panel).

Antiretroviral therapy was initiated by 2938 children (Table 1, lower panel). The median age at ART initiation was 81 (IQR, 36 to 125) months, with 291 children (9.9%) younger than 18 months, 839 (28.6%) aged 18 to 59 months, and 1808 (61.5%) 60 months or older. Compared with the overall cohort, children starting ART had lower CD4 cell percentage (11.8% vs 14.3%) and were more likely to be WHO stage III or IV (72.4% vs 53.3%). They otherwise did not differ substantially at baseline from the overall cohort with respect to sex, WAZ score, hemoglobin, and tuberculosis coinfection (Table 1).

Experience With First-Line Regimens: All Children

Of 2938 children starting ART, 1487 (50.6%) began stavudine plus lamivudine plus nevirapine, 1119 (38.1%)...
began zidovudine plus lamivudine plus nevirapine, 122 (4.2%) began zidovudine plus lamivudine plus efavirenz, and 210 (7.1%) began stavudine plus lamivudine plus efavirenz. Overall, 516 children (17.6%) were prescribed single-drug substitutions of their nucleoside reverse transcriptase inhibitor in response to drug intolerance, toxicity, or dosing issues. Of 1697 children prescribed stavudine, 171 (10.1%) switched from stavudine to zidovudine (switching rate, 10.2 per 100 patient-years; median time to switch, 183 [IQR, 68 to 378] days). Additionally, 345 of 1241 patients (27.8%) prescribed zidovudine switched from zidovudine to stavudine (switching rate, 27.9 per 100 patient-years; median time to switch, 112 [IQR, 43 to 270] days). Patients starting a zidovudine-based regimen were considerably more likely over time to have that drug substituted, compared with patients starting a stavudine-based regimen (HR, 2.8; 95% confidence interval [CI], 2.3 to 3.3). Of 2606 patients starting a nevirapine-based regimen, 225 (8.6%) switched to efavirenz (switching rate, 7.9 per 100 patient-years; median time to switch, 103 [IQR, 43 to 262] days).

**Survival Outcomes**

Of 2398 “active” children (ie, those not withdrawn from the program or late for follow-up; see “Methods”) receiving ART, 198 (8.3%) died over 3018 child-years of follow-up (6.6 deaths per 100 child-years; 95% CI, 5.7 to 7.5) (Table 2). Children who died were younger (median age, 46 [IQR, 19 to 120] months vs 84 [IQR, 41 to 125] months; P < .001), had lower median WAZ scores (−3.5 [IQR, −4.5 to −2.2] vs −2.1 [IQR, −3.2 to −1.1]; P < .001), had lower baseline median hemoglobin concentration (9.1 [IQR, 8.0 to 10.9] g/dL vs 10.2 [IQR, 9.1 to 11.4] g/dL; P < .001), were more likely to be WHO clinical stage III or IV (85% vs 71%, P < .001), were more likely to be in the 90th percentile for nonadherence (12.6% vs 7.8%, P = .02), and had greater immunosuppression at ART initiation when compared with those who survived (CD4 cell percentage, 10.0% [IQR, 4.6% to 14.5%] vs 12.0% [IQR, 7.5% to 17.6%]; P < .001).

Early mortality was higher than later mortality: of the 198 children who died, 112 (56.6%) died within 90 days of starting ART (90-day mortality rate, 17.4 per 100 child-years; 95% CI, 14.4 to 21.0), while an additional 86 children died after this initial period (post-

### Table 1. Characteristics of Children at Presentation and When Starting Antiretroviral Therapy (ART), Zambia (May 2004-July 2007)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Ages</th>
<th>Age &lt;18 mo</th>
<th>Age 18-59 mo</th>
<th>Age ≥60 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-age z score, median (IQR)a</td>
<td>3909</td>
<td>−2 (−3.2 to −0.9)</td>
<td>739 −1 (−3.0 to 0.1)</td>
<td>1119 −2.1 (−3.4 to −0.9)</td>
</tr>
<tr>
<td>CD4 cell percentage, median (IQR)</td>
<td>3384</td>
<td>14.3 (8.4 to 21.7)</td>
<td>455 18.3 (12.2 to 26.4)</td>
<td>1029 15.6 (9.8 to 23.8)</td>
</tr>
<tr>
<td>CD4 cell count, median (IQR), cells/µL</td>
<td>3640</td>
<td>363 (165 to 649)</td>
<td>445 651 (346 to 1087)</td>
<td>1071 532 (288 to 848)</td>
</tr>
<tr>
<td>Hemoglobin, median (IQR), g/dL</td>
<td>3435</td>
<td>10.2 (8.9 to 11.4)</td>
<td>451 9.4 (8.1 to 10.7)</td>
<td>1031 9.8 (5.5 to 10.9)</td>
</tr>
<tr>
<td>Tuberculosis (active), %</td>
<td>243</td>
<td>5.7</td>
<td>32 3.9</td>
<td>67 5.6</td>
</tr>
<tr>
<td>WHO stage III or IV, %</td>
<td>2160</td>
<td>53.3</td>
<td>334 50.3</td>
<td>643 54.5</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; WHO, World Health Organization.

aCalculated from standardized growth charts (see “Methods”).

bPercentage of total lymphocytes.
90-day mortality rate, 2.9 per 100 child-years; 95% CI, 2.3 to 3.6) (Table 2).

In both crude and multivariate Cox proportional hazards regression, the hazard of death was associated with CD4 cell depletion, lower WAZ score, anemia, nonadherence, and age (Table 3). Compared with those having a WAZ score greater than –1, children with WAZ scores greater than –3 or less (adjusted HR, 1.8; 95% CI, 1.1 to 2.7) were more likely to die (adjusted HR, 1.6; 95% CI, 1.0 to 2.4) were more likely to die, while those who were in the 90th percentile for nonadherence were more likely to die than those below the 90th percentile (adjusted HR, 1.6; 95% CI, 1.0 to 2.5). Patient sex, prevalent tuberculosis, serum creatinine at entry, baseline WHO clinical stage, and initial drug regimen ( stavudine- vs zidovudine-based) were not significantly associated with death.

In the overall analysis, there was an inverse relationship between child age and mortality risk; for each additional year of age, we observed an approximate 10% reduction in the hazard of death (adjusted HR, 0.90; 95% CI, 0.87 to 0.94) (Table 3).

**Survival: Children Younger Than 18 Months**

Of 223 active children younger than 18 months receiving ART, 45 (20.2%) died over 213 child-years of follow-up (mortality rate, 21.1 deaths per 100 child-years; 95% CI, 15.4 to 28.2) (Table 2). Mortality within 90 days of starting therapy was especially high in this group (52.2 deaths per 100 child-years; 95% CI, 35.2 to 74.5). In both crude analysis and multivariate Cox proportional hazards regression, the hazard of death increased markedly with successively lower WAZ scores (Table 3, Figure 2) but only achieved statistical significance among children with WAZ scores of –3 or less (adjusted HR, 3.2; 95% CI, 1.2 to 8.7). There was also a suggestion that anemia at ART initiation was also associated with death. Compared with children having hemoglobin concentrations of 8 g/dL or greater, those with concentrations less than 8 g/dL were more likely to die (adjusted HR, 1.6; 95% CI, 1.0 to 2.4). Anemia at ART initiation was also associated with death. Compared with children having 20% or more CD4 cell percentage, children with 10% to less than 20% were more likely to die (adjusted HR, 1.4; 95% CI, 1.2 to 2.8). Patient sex, baseline hemoglobin concentration, baseline WHO clinical stage, adherence, prevalent tuberculosis, age, and initial drug regimen were not significantly associated with death among children younger than 18 months.

**Survival: Children Aged 18 to 59 Months**

Of 672 active children aged 18 to 59 months receiving ART, 45 (6.6 per 100 child-years; 95% CI, 4.5 to 9.8) died over 1,967 child-years of follow-up (mortality rate, 7.6 deaths per 100 child-years; 95% CI, 5.9 to 9.8) (Table 2). In both crude analysis and multivariate Cox proportional hazards regression, the hazard of death increased with successively lower WAZ scores (Table 3, Figure 2) but only achieved statistical significance among children with WAZ scores of –3 or less (adjusted HR, 3.2; 95% CI, 1.2 to 8.7). There was also a suggestion that anemia at ART initiation was also associated with death. Compared with children having hemoglobin concentrations of 8 g/dL or greater, those with concentrations less than 8 g/dL were more likely to die (adjusted HR, 1.6; 95% CI, 1.0 to 2.4). Anemia at ART initiation was also associated with death. Compared with children having 20% or more CD4 cell percentage, those with values of 10% to less than 20% were more likely to die (adjusted HR, 1.8; 95% CI, 1.2 to 2.8). Patient sex, baseline hemoglobin concentration, baseline WHO clinical stage, adherence, prevalent tuberculosis, age, and initial drug regimen were not significantly associated with death among children aged 18 to 59 months.

**Survival: Children Aged 60 Months or Older**

Of 2398 active children aged 60 months or older receiving ART, 198 (8.1 per 100 child-years; 95% CI, 6.6 to 9.8) died over 3,018 child-years of follow-up (mortality rate, 7.3 deaths per 100 child-years; 95% CI, 5.0 to 9.6) (Table 2). In both crude analysis and multivariate Cox proportional hazards regression, the hazard of death increased with successively lower WAZ scores (Table 3, Figure 2) but only achieved statistical significance among children with WAZ scores of –3 or less (adjusted HR, 2.0; 95% CI, 1.5 to 2.7). There was also a suggestion that anemia at ART initiation was also associated with death. Compared with children having hemoglobin concentrations of 8 g/dL or greater, those with concentrations less than 8 g/dL were more likely to die (adjusted HR, 1.6; 95% CI, 1.0 to 2.4). Anemia at ART initiation was also associated with death. Compared with children having 20% or more CD4 cell percentage, those with values of 10% to less than 20% were more likely to die (adjusted HR, 1.5; 95% CI, 1.1 to 1.9). Patient sex, baseline hemoglobin concentration, baseline WHO clinical stage, adherence, prevalent tuberculosis, age, and initial drug regimen were not significantly associated with death among children aged 60 months or older.
years; 95% CI, 3.6-5.6) (Table 2). In both crude analysis and multivariate Cox proportional hazards regression, the hazard of death among children 60 months or older was associated with anemia (Table 3, Figure 2). Compared with children having a baseline hemoglobin concentration of 8 g/dL or greater, those with baseline concentrations less than 8 g/dL were more likely to die (adjusted HR, 2.0; 95% CI, 1.1 to 3.8). There was also a suggestion of

### Table 3. Factors Associated With Mortality in Children Receiving Antiretroviral Therapy by Age Category in Zambia (May 2004-July 2007)

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Ages</th>
<th>Age &lt;18 mo</th>
<th>Age 18-59 mo</th>
<th>Age ≥60 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1149 1.0 (0.8-1.3)</td>
<td>98 1.0 (0.5-1.7)</td>
<td>372 1.0 (0.6-1.6)</td>
<td>751 1.0 (0.6-1.4)</td>
</tr>
<tr>
<td>Male</td>
<td>1249 1.0 (0.6-1.2)</td>
<td>125 0.9 (0.3-1.3)</td>
<td>413 1.0 (0.6-1.8)</td>
<td>505 1.0 (0.6-1.3)</td>
</tr>
<tr>
<td><strong>Weight-for-age z score</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥−1</td>
<td>494 1.0 (0.8-1.3)</td>
<td>100 1.0 (0.6-1.6)</td>
<td>325 1.4 (0.9-2.0)</td>
<td>620 1.0 (0.6-1.4)</td>
</tr>
<tr>
<td>&gt;−2 through −1</td>
<td>533 1.3 (0.7-2.5)</td>
<td>32 1.9 (0.3-11.5)</td>
<td>129 2.5 (0.9-6.6)</td>
<td>240 1.4 (0.6-3.3)</td>
</tr>
<tr>
<td>&gt;−3 through −2</td>
<td>504 2.2 (1.2-4.1)</td>
<td>25 6.1 (1.3-27.7)</td>
<td>139 2.5 (0.9-6.6)</td>
<td>325 1.4 (0.6-3.3)</td>
</tr>
<tr>
<td>≤−3</td>
<td>746 3.9 (2.2-6.6)</td>
<td>38 7.9 (2.3-40.9)</td>
<td>207 5.1 (2.2-12.2)</td>
<td>460 3.2 (1.5-6.8)</td>
</tr>
<tr>
<td><strong>CD4 cell percentage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>386 1.0 (0.9-2.1)</td>
<td>52 1.0 (0.2-2.2)</td>
<td>154 1.0 (0.2-2.2)</td>
<td>200 1.0 (0.7-2.9)</td>
</tr>
<tr>
<td>10 to &lt;20</td>
<td>897 1.4 (1.1-3.1)</td>
<td>96 4.7 (1.4-15.7)</td>
<td>283 1.4 (0.6-3.1)</td>
<td>518 0.7 (0.4-1.3)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>810 1.8 (1.2-2.7)</td>
<td>37 5.2 (1.4-18.8)</td>
<td>192 2.0 (0.9-4.4)</td>
<td>581 1.5 (0.9-2.6)</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>1886 1.0 (1.6-3.1)</td>
<td>152 1.0 (0.3-1.7)</td>
<td>109 1.0 (0.3-1.7)</td>
<td>1209 1.0 (1.1-3.8)</td>
</tr>
<tr>
<td>&lt;8</td>
<td>274 2.2 (1.0-2.4)</td>
<td>41 1.2 (0.3-1.7)</td>
<td>93 2.0 (1.1-3.6)</td>
<td>140 2.5 (1.4-4.2)</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2218 1.0 (0.6-1.6)</td>
<td>204 1.0 (0.2-2.2)</td>
<td>46 0.4 (0.1-1.7)</td>
<td>115 1.4 (0.7-2.9)</td>
</tr>
<tr>
<td>Active</td>
<td>180 0.9 (0.9-2.1)</td>
<td>19 0.7 (0.2-2.2)</td>
<td>46 0.4 (0.1-1.7)</td>
<td>115 1.4 (0.7-2.9)</td>
</tr>
<tr>
<td>WHO stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>649 1.0 (0.6-1.8)</td>
<td>40 1.0 (0.5-5.5)</td>
<td>24 1.2 (0.4-3.9)</td>
<td>120 1.1 (0.5-2.2)</td>
</tr>
<tr>
<td>III and IV</td>
<td>1703 2.4 (0.6-1.1)</td>
<td>157 1.5 (0.6-1.8)</td>
<td>52 0.8 (0.3-2.0)</td>
<td>111 1.5 (0.8-3.0)</td>
</tr>
<tr>
<td><strong>Creatinine, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.7</td>
<td>1586 1.0 (0.6-1.1)</td>
<td>149 1.0 (0.5-5.5)</td>
<td>439 1.0 (0.3-2.3)</td>
<td>908 1.0 (0.8-3.0)</td>
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<tr>
<td>&gt;0.7</td>
<td>154 1.1 (0.6-1.8)</td>
<td>10 1.7 (0.5-5.5)</td>
<td>24 1.2 (0.4-3.9)</td>
<td>120 1.1 (0.5-2.2)</td>
</tr>
<tr>
<td><strong>Nonadherence, percentile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90th</td>
<td>2201 1.0 (0.6-1.8)</td>
<td>189 1.0 (0.5-5.5)</td>
<td>620 1.0 (0.3-2.3)</td>
<td>1392 1.0 (0.8-3.0)</td>
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<tr>
<td>≥90th</td>
<td>197 2.0 (1.0-2.4)</td>
<td>34 1.8 (0.6-3.3)</td>
<td>52 0.8 (0.3-2.3)</td>
<td>111 1.5 (0.7-3.2)</td>
</tr>
<tr>
<td><strong>Initial regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine-based</td>
<td>1389 1.0 (0.6-1.1)</td>
<td>132 1.0 (0.6-1.8)</td>
<td>413 1.0 (0.5-1.1)</td>
<td>844 1.0 (0.5-1.1)</td>
</tr>
<tr>
<td>Zidovudine-based</td>
<td>1009 0.8 (0.6-1.1)</td>
<td>91 1.0 (0.6-1.5)</td>
<td>259 0.9 (0.5-1.1)</td>
<td>659 0.7 (0.3-2.0)</td>
</tr>
<tr>
<td><strong>Age, per year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>2398 0.9 (0.8-0.95)</td>
<td>223 1.90 (0.87-4.12)</td>
<td>672 0.62 (0.47-0.87)</td>
<td>1503 1.06 (0.90-1.14)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; WHO, World Health Organization. Reference values are abbreviated as 1.0.

SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.

All HRs were calculated from Cox proportional hazards regression models using partial likelihood method.

Calculated from standardized growth charts (see “Methods”).

Percentage of total lymphocytes.

Dichotomized at 8.0 g/dL based on prior convention.

These factors failed to meet criteria for inclusion in multivariate regression models (see “Methods”).

WHO stages I and II were combined to accommodate small patient numbers in stratified analyses. WHO stages III and IV were combined to accommodate a definition change that occurred during the course of the study (see “Methods”).

Dichotomized at 90th percentile based on prior convention.

Age was treated as a continuous variable in the models, with a unit of years. Age-associated HRs are reported to 2 decimal places to allow for precision with these small, but in some cases statistically significant, findings.
an association between both severe CD4 cell depletion and very low weight-for-age and death. Compared with children having a CD4 cell percentage of 20% or more, those with values less than 10% trended toward a higher likelihood of death (adjusted HR, 2.0; 95% CI, 0.9 to 4.1), as did those with a WAZ score of −3 or less when compared with those having a WAZ score greater than −1 (adjusted HR, 1.8; 95% CI, 0.8 to 4.3). Patient age was associated with mortality in this age group. For each additional year of child age there was an 8% increase in associated hazard of mortality (adjusted HR, 1.08; 95% CI, 0.99 to 1.17). Patient sex, baseline WHO clinical stage, adherence, prevalent tuberculosis, and initial drug regimen were not significantly associated with death among children 60 months or older.

**CD4 Cell Response, Weight Gain, and Hemoglobin Response**

Overall, children receiving ART showed significant improvements in CD4 cell status, weight gain, and hemoglobin concentration. The CD4 cell response analysis was limited to 1561 children who had a baseline and at least 1 repeat measurement. The mean CD4 cell percentage at ART initiation was 12.9% (95% CI, 12.5% to 13.3%) and increased to 23.7% (95% CI, 23.1% to 24.3%) at 6 months among the 1246 of 1561 (79.8%) active children who had been enrolled long enough to have a 6-month measurement, to 27.0% (95% CI, 26.3% to 27.6%) at 12 months among the 862 of 1147 (75.2%) children enrolled long enough to have a 12-month measurement, to 28.0% (95% CI, 27.2% to 28.8%) at 18 months among the 628 of 800 (78.5%) children enrolled long enough to have an 18-month measurement, and to 28.4% (95% CI, 27.4% to 29.4%) at 24 months among the 413 of 502 (82.3%) children enrolled long enough to have a 24-month measurement (FIGURE 3).

Similarly, a substantial increase was noted in absolute CD4 cell count. The mean CD4 cell count at ART initiation among the 1178 children 60 months or older who had at least 1 repeat measurement was 284 cells/µL.
(95% CI, 270 to 299) and increased to 564 cells/µL (95% CI, 541 to 586) at 6 months among the 990 of 1178 (84.0%) who had been enrolled long enough to have a 6-month measurement, to 635 cells/µL (95% CI, 606 to 663) at 12 months among the 667 of 884 (75.5%) who had been enrolled long enough to have a 12-month measurement, to 711 cells/µL (95% CI, 675 to 747) at 18 months among the 506 of 640 (79.1%) who had been enrolled long enough to have an 18-month measurement, and to 660 cells/µL (95% CI, 618 to 703) at 24 months among the 342 of 415 (82.4%) who had been enrolled long enough to have a 24-month measurement (Figure 3).

The mean baseline hemoglobin concentration for the 1653 children starting ART who had at least 1 repeat measurement was 10.3 g/dL (95% CI, 10.2 to 10.4) and increased to 11.3 g/dL (95% CI, 11.2 to 11.4) at 6 months, 11.8 g/dL (95% CI, 11.6 to 11.9) at 12 months, 12.1 g/dL (95% CI, 12.0 to 12.3) at 18 months, and 12.2 g/dL (95% CI, 12.1 to 12.4) at 24 months.

**Figure 3.** Changes in Weight-for-Age z Score, CD4 Cell Percentage and Absolute Count, and Hemoglobin Concentration for Children Receiving Antiretroviral Therapy, Zambia (May 2004–July 2007)

Analysis restricted to children with ≥1 repeat measure. Error bars indicate 95% confidence intervals. Baseline indicates the time at which antiretroviral therapy was initiated.
C1, 12.0 to 12.4) at 24 months (Figure 3). The mean baseline WAZ score for 1926 children starting ART who had at least 1 repeat measurement was −2.2 (95% CI, −2.2 to −2.1) and increased to −1.8 (95% CI, −1.9 to −1.7) at 6 months of therapy, to −1.6 (95% CI, −1.7 to −1.6) at 12 months, to −1.5 (95% CI, −1.6 to −1.4) at 18 months, and to −1.5 (95% CI, −1.6 to −1.4) at 24 months (Figure 3).

COMMENT

This early experience suggests that good clinical outcomes can be obtained treating children with ART at primary health care facilities in Zambia using predominately nonphysician clinicians. Mortality within the first 90 days of starting therapy was high, especially among the infants younger than 18 months. Although many children were extremely ill at presentation, those who survived past the first 90 days of therapy generally had good outcomes thereafter, a phenomenon that has been observed among adults in other developing-world settings. Among the younger children (<60 months), mortality was associated with decreasing WAZ score, while among older children (≥60 months), mortality was associated with anemia. As has been described in smaller cohorts in the region, we found that surviving children generally have very good CD4 cell responses. The average child in the cohort experienced a more than doubling of his or her CD4 cell percentage in the first year of ART (from a mean of 12.9% at treatment initiation to 27.0% at 12 months of therapy). Improvement in weight was more pronounced in the 2 younger age groups, with the average child gaining approximately 1 SD in his or her WAZ score compared with the older children, in whom the improvements were evident but more modest.

This is, to our knowledge, the largest developing-world cohort of children receiving ART to be described and possibly the only published report to date on ART outcomes among children treated in a setting without pediatric specialty expertise. The ability of the Zambian Ministry of Health to scale up these services so quickly can be attributed to several key factors. First, there has been an early and explicit government commitment to pediatric AIDS care in Zambia, including early guideline establishment, procurement of pediatric drug formulations, and, with support from the US Centers for Disease Control and Prevention and Columbia University, establishment of a center of excellence for pediatric HIV training and referral at the University Teaching Hospital. Second, the decision to decentralize care and allow HIV-infected children to be treated by nonphysician clinicians in primary health centers has allowed a much larger segment of the population to be reached. Third, partnerships with donor organizations, like PEPFAR and the Global Fund, and with partners in the field, has allowed an exceedingly underresourced health care system to develop high-quality and effective AIDS treatment services for a large number of children in Lusaka.

Approximately half of the children in this cohort were more than 2 SDs below their expected weight-for-age. Progressively lower WAZ scores were associated with progressively higher mortality rates, especially in younger children. These findings are consistent with other, smaller studies in the region. Multiple factors likely contribute to the cohort’s extremely low weight-for-age at entry, including chronic infections (eg, intestinal helminthiasis, tuberculosis), poverty, and food insecurity. One study in Lusaka found that a quarter of breastfeeding mothers reported completely running out of food at least 1 day per month. In areas where infant diagnostics are not available, poor growth may be a critical indicator for starting ART. Further, our observation that many of the older children are also underweight suggests that infants are not the only ones not being recognized as infected and calls for more widespread testing of children at different entry points (eg, malnutrition programs, pediatric wards, tuberculosis programs, adult ART programs). Because of the high prevalence of malnutrition among these HIV-infected children, nutritional supplementation for both infant and mother should also be investigated as a potential adjuvant to ART, especially during the critical weeks after initiation, when the children are at highest risk for mortality.

As previously observed among HIV-infected adults in Lusaka, prevalent tuberculosis was not associated with an increased mortality risk among children in this cohort. We believe this observation to be attributable to 2 major causes. First, the capacity for tuberculosis diagnosis (and the exclusion of tuberculosis immune reconstitution disease) in the Lusaka primary health care setting is limited, especially among children, in whom sputum collection can be particularly challenging. Second, most children categorized as having prevalent tuberculosis were already receiving antituberculosis treatment prior to their enrollment in the ART program and were therefore probably stable while receiving antituberculosis treatment before entering the analysis cohort. These findings reiterate the need for feasible and affordable methods for tuberculosis screening among patients with HIV, regardless of their age.

The age distribution of our cohort (median age, 65 months) reflects both the natural progression of HIV in children and the difficulties inherent in early diagnosis of children in resource-limited settings. In Lusaka, the recent implementation of virologic diagnostic testing in postnatal and pediatric clinics should improve the ability to identify HIV-infected infants earlier in life and screen them for initiation of ART. In rural areas outside the capital city, however, cost-effective and feasible algorithms are still urgently needed to identify treatment-eligible HIV-infected infants. It is likely that a majority of younger infected children die...
prior to diagnosis from illnesses not recognized as HIV-related (eg, gastrointestinal, pneumonia) and that this leads to underrepresentation of this age group in our cohort. Thus, our findings may be somewhat less generalizable to settings in which a majority of patients are referred as infants from failed perinatal prophylaxis programs. Our high losses to follow-up for children not requiring ART at initial presentation is a related and concerning issue. In light of the recently reported very high mortality rates in infected infants without obvious immunosuppression, it is likely that many of these children are dying at home. This highlights the urgent need for better diagnostic capacity and linkages between mother-to-child HIV prevention programs and pediatric ART.

Despite the wide availability of ART since 2004, only approximately 7% of Lusaka’s public-sector ART patients are younger than 16 years, a proportion well below the target of 10% to 15% set by the WHO. The reasons for the lag in enrollment of children are complex and numerous but potentially include clinic environments that are not “child friendly,” staff members who lack sufficient training in pediatric AIDS care, negative community perceptions about treatment of HIV-infected children, and of course the very high mortality rates among infected children younger than 2 years. To reach international pediatric treatment goals, there must be concerted and focused effort toward building pediatric clinical capacity through training, skills building, and mentorship. It is likely that community education efforts will need to be redoubled as well.

In summary, our early experience in Lusaka demonstrates that scale-up of pediatric ART services with good clinical outcomes is feasible in African primary care facilities. Decentralized services can play an important role complementary to that of the specialty center and in Lusaka have achieved clinical and immunologic outcomes comparable to those seen in the more industrialized world. Mortality is highest among underweight children and those who are severely immunosuppressed. These findings indicate the critical need for earlier diagnosis and referral of HIV-infected children. Of course, the ultimate solution to the problem of pediatric AIDS lies in prevention of mother-to-child transmission and in preventing primary infection in women.

Author Affiliations: Centre for Infectious Disease Research in Zambia, Lusaka (Dr. Bolton-Moore, Mubiana-Mbewe, Chintu, E. Stringer, Chi, Kankasa, Levy, and J. Stringer and Mr. Cantrell); Schools of Medicine and Public Health, University of Alabama at Birmingham (Dr. E. Stringer, Chi, Sinkala, Wilson, and J. Stringer and Mr. Cantrell); University Teaching Hospital, Lusaka (Dr. Kankasa); Zambia Ministry of Health, Lusaka (Dr. Sinkala and Mwango); Elizabeth Glaser Pediatric AIDS Foundation, Santa Monica, California (Dr. Wilfert); Columbia University College of Physicians and Surgeons, New York, New York (Dr. Abrams); and US Centers for Disease Control and Prevention, Global AIDS Program, Lusaka (Dr. Bulterys). The findings and conclusions in this article have not been subjected to agency review. The Centers for Disease Control and Prevention had no role in data collection, analysis, or interpretation of data.


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Previous Presentation: These data were presented in part (Children enrolled in a public HIV care and treatment program in Lusaka, Zambia: rapid scale-up and first-year clinical outcomes [abstract MoAB0201]) at the XVI International AIDS Conference; August 13-18, 2006; Toronto, Ontario, Canada.

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