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Incidence of WHO Stage 3 and 4 Events, Tuberculosis, and Mortality in Untreated, HIV-Infected Children Enrolling in Care Before 1 Year of Age: An Iedea (International Epidemiologic Databases To Evaluate AIDS) East Africa Regional Analysis

Andrea Ciaranello, MD, MPH[1], **Zhigang Lu, MD**[2], **Samuel Ayaya, MBCHB, MMed**[3], **Elena Losina, PhD**[2,4], **Beverly Musick, MS**[5], **Rachel Vreeman, MD, MS**[6], **Kenneth A. Freedberg, MD, MSc**[1,2], **Elaine J. Abrams, MD**[7], **Lisa Dillabaugh, MD**[8], **Katie Doherty, BA**[2], **John Ssali, MD**[9], **Constantin T. Yiannoutsos, PhD**[5], and **Kara Wools-Kaloustian, MD, MSc**[10]

[1]Division of Infectious Diseases and Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA, USA [2]Division of General Medicine and Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA, USA [3]Department of Child Health and Paediatrics, Moi University School of Medicine, Eldoret, KENYA [4]Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA [5]Department of Biostatistics, Indiana University, Indianapolis, IN, USA [6]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA [7]ICAP, Mailman School of Public Health, Columbia University and College of Physicians & Surgeons, Columbia University, NY, USA [8]Family AIDS Care and Education Service (FACES) program, Kisumu, KENYA, and Department of Pediatrics, University of California, San Francisco, CA, USA [9]Masaka Regional Referral Hospital, AHF-Uganda Cares Masaka, Uganda [10]Division of Infectious Disease, Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

Background—Few studies have reported CD4%- and age-stratified rates of WHO Stage 3 (WHO3) events, WHO Stage 4 (WHO4) events, tuberculosis (TB), and mortality in HIV-infected infants before initiation of antiretroviral therapy (ART).

Methods—HIV-infected children enrolled before 1 year of age in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) East Africa region (10/01/2002-11/30/2008) were included. We estimated incidence rates of earliest clinical event (WHO3, WHO4, and TB), prior to ART initiation per local guidelines, stratified by current age (< or ≥6 months) and current

Corresponding Author: Andrea L. Ciaranello, MD, MPH, Division of Infectious Diseases and Medical Practice Evaluation Center, Massachusetts General Hospital, 50 Staniford Street, Room 920, Boston, Massachusetts 02114, Tel: (617) 643-7540 Fax: (617) 726-2691 aciaranello@partners.org.

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ETHICS: This work was approved by the Columbia University Medical Center Institutional Review Board, the Indiana University Institutional Review Board, the Kenya Medical Research Institute (KEMRI) National Ethics Review Committee, the Moi Teaching and Referral Hospital/Moi University Institutional Research and Ethics Committee, the Moi University School of Medicine IREC, the Partners Healthcare IRB (Boston, MA), the St. Francis Hospital Nsambya IREC, the Uganda National Council for Science and Technology, and the University of California San Francisco Human Research Protection Program Committee on Human Research.

CD4% (<15%, 15–24%, ≥25%). CD4%-stratified mortality rates were estimated separately for children who did not experience a clinical event ("background" mortality) and for children who experienced an event, including "acute" mortality (≤30 days post-event) and "later" mortality (>30 days post-event).

Results—Among 847 children (median enrollment age: 4.8 months; median pre-ART follow-up: 10.8 months; 603 (71%) with ≥1 CD4% recorded), event rates were comparable for those aged <6 and ≥6 months. Current CD4% was associated with risk of WHO4 events for children <6 months old, and with all evaluated events for children ≥6 months old ($p<0.05$). "Background" mortality was 3.7–8.4/100py. "Acute" mortality (≤30 days post-event) was 33.8/100py (after TB) and 41.1/100py (after WHO3 or WHO4). "Later" mortality (>30 days post-event) ranged by CD4% from 4.7–29.1/100py.

Conclusions—In treatment-naïve, HIV-infected infants, WHO3, WHO4, and TB events were common before and after 6 months of age and led to substantial increases in mortality. Early infant HIV diagnosis and treatment are critically important, regardless of CD4%.

Keywords

Pediatric HIV; opportunistic infection; morbidity; mortality

Morbidity and mortality among HIV-infected children is high in the absence of antiretroviral therapy (ART), with as many as 50% of children estimated to die before age two.[1–3] Data from the Children with HIV Early Antiretroviral Therapy (CHER) clinical trial in South Africa demonstrated a 75% reduction in morbidity and 76% reduction in mortality if ART was initiated for HIV-infected infants before three months of age, compared to deferral of ART until immunologic or clinical criteria were met.[4] The World Health Organization (WHO) now recommends ART for all HIV-infected children <5 years of age, regardless of clinical status or CD4 percentage (CD4%).[5,6]

Access to ART for HIV-infected children remains very low in most resource-limited settings. Despite scale-up in the absolute number of children receiving ART, only 23% of ART-eligible children were estimated to be receiving ART in low- and middle-income countries in 2010.[7] Symptom-based algorithms for infant HIV diagnosis have limited sensitivity, and routine initiation of ART in HIV-infected infants requires PCR-based testing to diagnose HIV infection in the first year of life; delays in early infant diagnosis and ART initiation are therefore common.[6,8,9] As critical efforts to improve infant HIV diagnosis and access to pediatric ART are underway, detailed knowledge of the clinical risks faced by infants and children awaiting access to ART can inform clinical monitoring and prophylaxis strategies.

Most available data on the risks of opportunistic infections and tuberculosis (TB) among HIV-infected children prior to ART initiation are from the pre-ART era, report on small numbers of children, and are not stratified by CD4%; those that examine the impact of age rely on age at enrollment, rather than age at the time of occurrence of clinical events.[2,3,10–16] Furthermore, the timing of mortality with respect to preceding opportunistic infections and TB has not been well described.[2,3,10–16] Many reports are also limited to children who

survive to enroll in care well after infancy, introducing an important "survivorship" bias.[17,18] Our objectives were: 1) to report incidence rates of WHO Stage 3, WHO Stage 4, and TB events among children enrolling care before one year of age, stratified by CD4% and age at the time of each event, and 2) to examine the impact of these clinical events on the incidence and timing of infant mortality.

METHODS

IeDEA clinical sites

The International Epidemiologic Databases to Evaluate AIDS (IeDEA) is a worldwide consortium of AIDS care and treatment centers. Seven programs from Kenya, Uganda, and Tanzania within the IeDEA East African Region contributed data for this analysis: the Academic Model Providing Access to Healthcare (AMPATH) program, the Family AIDS Care and Education Service (FACES) program, two Tanzanian Ministry of Health (MOH) sites, and three sites in the MTCT-Plus Initiative (further details in Supplemental Appendix).[19–22] During the study period (2002–2008), IeDEA East Africa programs attempted to initiate ART for all children meeting WHO ART eligibility criteria at the time (combinations of clinical, age, and CD4% criteria). Although HIV DNA PCR testing for early infant HIV diagnosis was available to all sites, delays in receipt of PCR results and occasional shortages of PCR test kits led to delayed diagnosis and ART initiation for some children.

Eligible participants, diagnostic criteria, and data collection

HIV-infected children were eligible for inclusion if they enrolled in care at any of the participating IeDEA sites from October 2002 through November 2008 and before 12 months of age. A diagnosis of HIV infection was made if a child had a positive HIV Enzyme Immunoassay (EIA) recorded after 15 months of age, or if at least two clinical or immunologic criteria were met (Appendix).

Diagnoses were recorded in the medical records based on methods available in routine clinical care at each site, including clinical, radiographic, laboratory, and pathologic evaluations. With the exception of TB, clinical events were categorized by 2010 WHO staging criteria as Stage 3 (WHO3) or Stage 4 (WHO4).[6] Chart-recorded diagnoses of pulmonary, lymph node, and extrapulmonary TB were included in a separate and mutually exclusive category of TB; this category also included documented prescription of anti-tuberculous medications (excluding isoniazid as monotherapy). For this analysis, observations commenced upon patient enrollment into care and terminated at initiation of ART or, for those who did not begin ART, date of death or the last recorded visit date. Data collection and data harmonization procedures are further described in the Appendix.

Statistical analysis

Descriptive statistics (frequencies) were used to describe demographic characteristics of the cohort, including age at enrollment, sex, baseline CD4% values, prior receipt of maternal or neonatal medications for prevention of mother-to-child transmission (PMTCT), use of cotrimoxazole prophylaxis against opportunistic infections, and length-for-age, weight-for-

age, and weight-for-height Z-scores at enrollment.[23] Characteristics of children with and without CD4% data were compared using Chi-square tests for proportions and Kruskal-Wallis and log-rank tests for continuous variables.

Description of earliest WHO3, WHO4, TB, and overall events—We described the number of children experiencing at least one WHO3, WHO4, or TB event, defined separately for each event category. For example, “earliest WHO3 event” refers to the first recorded diagnosis of a WHO Stage 3 condition. "Earliest overall event" was defined as the first event in any of the three categories (WHO3, WHO4, or TB).

Incidence rates of earliest WHO3, WHO4, TB, and overall events—Incidence rates of earliest WHO3, WHO4, and TB events prior to ART initiation were calculated separately, using incidence density analysis. Following a first WHO3 event, for example, patients remained at risk for WHO4 and TB events, but subsequent WHO3 events were excluded. If patients experienced multiple WHO3 events on the date of their first WHO3 event, they were considered to experience only one "earliest" WHO3 event for the incidence rate analysis. The incidence rate of earliest overall event defined the first event as a diagnosis in any of the three categories (WHO3, WHO4, or TB).

Incidence rates of earliest events were stratified by current age < or ≥6 months, defined as age at the time of each clinical event. In order to include prevalent conditions at the time of enrollment in care, or recorded history of events prior to enrolment, we considered time at risk to begin at birth (for the "current age <6 months" analysis), and at 6 months of age (for the "current age ≥6 months" analysis). Incidence rates were further stratified by current CD4%, defined as CD4% at or near the time of event. CD4% was categorized as CD4<15%, 15–24%, ≥25% for children with at least one recorded CD4% value prior to ART initiation, and as "missing" for children with no recorded CD4% data. Only CD4% values prior to ART initiation were analyzed. Methods for estimating current CD4% are described in the Appendix.

Events and time at risk were censored at ART initiation, last recorded visit, or death. Confidence intervals of incidence rates were based on logarithmic transformation of the rates to guarantee that no interval bound would be below 0 or above 100%. We compared event rates between age and CD4 strata using test of trend analyses within a log-linear (Poisson) regression model, excluding missing CD4% values, assessed by the Wald test with p-values <0.05 considered statistically significant.

Mortality—Overall mortality rates were described separately for children who did and did not experience a clinical event during the follow-up period. For children who did not experience a WHO3, WHO4, or TB event, we calculated a “background” mortality rate; time at risk was defined as time from birth (for children enrolling at <6 months of age) or at 6 months of age (for children enrolling at ≥6 months of age) until ART initiation, death, or last visit.

For children who did experience a clinical event, two types of mortality rates were described. We first calculated an “acute” mortality rate, defined as the rate of death within

30 days following each type of event (WHO3/WHO4, or TB). Each child experiencing an event contributed risk up to 30 days after the event or until death, ART initiation, database closure, or last visit date, whichever occurred first. We next estimated a "later" mortality rate, defined as the rate of death occurring >30 days after a WHO3/WHO4 or TB event. This analysis was limited to children who experienced an event and did not die within 30 days. Children were excluded from this mortality rate calculation if, within 30 days of the clinical event, ART was started, care was discontinued, or the database was closed. Time at risk was defined to begin 30 days after the event, and to extend until death, ART initiation, database closure, or last visit date, whichever occurred first. All mortality rates were stratified by current CD4% for children with at least one recorded CD4% value, as described above. Confidence intervals were constructed based on log-transformed mortality rates to ensure a range of 0–100%.

RESULTS

The cohort included 847 children who enrolled in care at IeDEA East Africa clinical sites before 1 year of age. Demographic and baseline characteristics are shown in Table 1. Median age at enrollment was 4.8 months, and 52% of patients were female. At least one pre-ART CD4% value was recorded for 603 children (71%). ART was initiated in 391 children (46%), 75 children (9%) died before ART initiation, and 133 (16%) were lost to follow-up, leading to a median duration of follow-up before ART initiation of 10.8 months (95% CI: 9.7–12.2 months). The remaining 248 children (29%) did not initiate ART prior to database closure.

Reflecting the study population of HIV-infected children, rates of prior receipt of medications for PMTCT were low. Of 702 mothers with data available, 174 (25%) received any form of maternal prophylaxis. Of 505 infants with data available, 200 (40%) received neonatal prophylaxis; a majority (172/200) received single-dose nevirapine alone. Almost all children (99%) received cotrimoxazole prophylaxis during the study period. Children with missing CD4% values did not differ from those with available CD4% data with regard to age, sex, HIV disease severity, or maternal receipt of medications for PMTCT ($p>0.05$). Children with available CD4% data had longer follow-up time recorded (12.3 months) than those without CD4% data (7.5 months, $p<0.001$).

Description of earliest WHO3, WHO4, TB, and overall events (Table 2)

Specific methods of diagnosis were not recorded for all clinical events in the database; available data are shown in Table 2. There were 613 children (72% of the cohort) who experienced an earliest overall event, defined as at least one event in any of the three diagnosis categories. Five hundred twenty children (61%) experienced at least one WHO3 event; the majority of earliest WHO3 events were related to bacterial meningitis, pneumonia or sepsis; oral candidiasis; chronic diarrhea; and moderate malnutrition (Table 2). Three hundred five children (36%) experienced at least one WHO4 event, primarily recurrent bacterial infections, wasting, *Pneumocystis jiroveci* pneumonia, and esophageal candidiasis. One hundred seventy-one children (20%) experienced at least one TB event; of the 155 TB

cases with available diagnoses, 141 (91%) were pulmonary TB. Of 1,082 recorded events, 264 (24 %) were documented to be present at enrollment in care (Table 2, right column).

Incidence rates of earliest WHO3, WHO4, TB, and overall events

Incidence rates for all three types of events were comparable among infants at current ages <6 months and ≥6 months (Figure 1; Supplemental Table A). Children with missing CD4% values contributed slightly more person-time at risk to the "current age <6 month" analysis (48.7 of 199.2 person-years (PY), or 24%) than to the "current age ≥6 months" analysis (92.4 of 447.1 PY, or 21%; Supplemental Table A). Incidence rates of earliest overall event ranged by CD4% from 69.6–117.7/100PY at ages <6 months, and 49.6–188.6/100PY at ages ≥6 months. Incidence rates of earliest WHO3 events were 63.9–101.8/100PY (<6 months) and 40.1–148.1/100PY (≥6 months). For earliest WHO4 events, incidence rates were 19.0–43.0/100PY (<6 months) and 16.8–78.7/100PY (≥6 months). For earliest TB events, incidence rates were 6.2–18.1/100PY (<6 months) and 9.4–46.3/100PY (≥6 months).

For children aged <6 months with at least one recorded CD4%, no statistically significant association was observed between current CD4% and earliest WHO3 events or TB events (Figure 1). At ages <6 months, however, CD4% was associated with earliest overall event and with earliest WHO4 events. For children aged ≥6 months, all evaluated events were associated with current CD4%. When both age strata were combined into a single analysis, CD4% remained statistically significantly associated with all evaluated events (not shown).

Mortality

The overall mortality rate for the cohort was 7.4/100PY (95% CI, 5.9–9.3/100PY; Table 3). Among children with no history of WHO3, WHO4, or TB events, the “background” mortality rate ranged from 3.7 (1.6–9.0)/100PY for CD4 >25% to 8.4 (3.8–18.7)/100PY for children with missing CD4% data. During the 30 days following recorded diagnoses of earliest clinical events, the “acute” mortality rate was 41.1 (25.5–66.0)/100PY after WHO3 or WHO4 events and 33.8 (12.7–90.0)/100PY after TB events. An increased risk of "later" mortality (>30 days after event diagnosis) was observed following any clinical event: mortality rates ranged from 4.7 (2.0–11.4)/100PY for children with CD4 ≥25% to 29.1 (16.9–50.2)/100PY for children with missing CD4% data.

DISCUSSION

The current study describes risks for WHO Stage 3 events, WHO Stage 4 events, TB, and mortality among East African, HIV-infected infants before initiation of ART. Our findings confirm that HIV-infected infants are at high risk for both disease progression and mortality, with these high risks persisting beyond the first six months of life. For infants <6 months of age, no association was observed between CD4% and risk of WHO3 or TB events. This may have been due to small numbers of very young infants, a slightly greater proportion of missing CD4% values among infants in the "current age <6 months" analysis, or presumed high pre-enrollment mortality among infants with low CD4%. For children >6 months of age, current CD4% stratum was associated with risks for all evaluated events. Missing CD4% data were associated with shorter follow-up durations, high event risks before age 6

months, and intermediate risks after age 6 months. This may reflect the impact of severe illness on reduced frequency of clinical care, as well as site-level differences in rates of HIV diagnostic testing, CD4% monitoring, and initiation of ART. Occurrence of a WHO3, WHO4, or TB event was associated with an increase in both acute mortality (<30 days from diagnosis) and sub-acute mortality (>30 days after diagnosis).

These results are derived from one of the largest reported cohorts of untreated, HIV-infected infants, and they confirm and extend previous work in four key ways. First, many studies have examined children enrolling well after one year of age, and are subject to survivorship bias (omitting clinical events occurring before enrollment, as well as early mortality precluding enrollment).[14,17,24,25] Second, available data on HIV-infected children <12–18 months of age are mainly limited to mortality rates,[1,15,18,26,27] and few analyses of WHO clinical events or CD4% values have been reported.[3,13,28,29] Third, studies reporting event rates do not stratify by CD4% or age, or stratify by baseline values rather than current values (most recent at the time of the clinical event).[3,13,28,29] Fourth, most available studies were conducted in the pre-ART era, often more than 10 years ago, reflecting infectious co-morbidities prevalent at that time.[1,2,13,15,18,27,29,30]

Our results demonstrate overall similar rates of events to those reported previously: at least one WHO3 event in 61% of children, and at least one WHO4 event in 36%, comparable to cumulative risks reported from Malawi, Rwanda, Zambia, and Thailand,[2,3,13,29] and rates of any first event at ages ≥6 months (49.6–188.6/100PY) similar to those reported from Haiti and Kenya.[28,31] These similar rates were observed despite two challenges: WHO stage was often recorded without specific clinical diagnoses (Table 2), preventing confirmation of the clinical stage designation, and data on secondary events within each WHO category were inconsistently recorded, limiting the analysis to first events in each category. Two specific diagnoses also merit attention. First, we recorded only 9 cases of HIV encephalopathy—perhaps lower than anticipated in untreated children due to limited ability to screen for and diagnose this condition.[32,33] Second, at least one TB event occurred in 20% of the cohort. Although lower than the 33% risk reported among untreated, HIV-infected children in South Africa, this still-substantial risk confirms the critical need to develop TB screening and prophylaxis protocols among HIV-infected infants not yet accessing ART.[34]

Despite similar rates of clinical events, we observed lower mortality in this cohort compared to prior literature. The overall mortality rate was 7.4/100PY, and this varied from a "background" mortality rate of 3.7–8.4/100PY among children with no history of WHO3, WHO4, or TB event, to a "later" mortality rate of 4.7–29.1/100PY among children with a history of such an event. In comparison, Newell *et al*. reported an overall mortality rate of 37.1/100PY in pooled data from several African trials, and Walker *et al*. reported rates of 14.7 and 44.5/100PY for Zambian children with WHO Stage 3 or 4 disease.[1,3] Other reported mortality risks, over varying follow-up durations, have ranged from a 12-month mortality risk of 26% in Rwanda to an 18-month risk of 69% in Côte d'Ivoire.[2,13,15,26,29,30] In our cohort, however, children experiencing a WHO Stage 3 or 4 event or a TB episode had very high acute mortality rates in the 30 days following these clinical events: 41.1/100PY after WHO3 or WHO4 and 33.8/100PY after TB; these rates are similar to other reported data. Of note, we observed particularly low mortality rates among children with no

history of clinical event, particularly those with CD4 >25% (3.7/100PY). This was explained by high event risks among these children, leaving a very small number with no event history eligible for this analysis. As expected, children with low CD4% had high mortality >30 days after clinical events.

Three factors may partially explain the low observed mortality rates. First, despite the early age at enrollment (median age, 4.8 months), survivor bias was not completely eliminated. Because children may have died before coming to care, we may have underestimated the true rates of clinical events and mortality; this effect is likely greatest for children presenting to care after 6 months of age. Nonetheless, these data represent one of the youngest reported cohorts of HIV-infected children yet described.[1–3,15,18,30] Second, given high rates of breastfeeding in a period before widespread postpartum prophylaxis, this cohort may include children infected with HIV during delivery or breastfeeding, for whom disease progression may be slower than among children with intrauterine infection.[35,36] Third, unlike children in the pre-ART era, many children in the IeDEA cohort were able to access and initiate ART once they met the clinical and CD4% criteria suggested by WHO guidelines at the time of their care. As a result, after a first WHO3 or WHO4 event, 54% of children in this cohort initiated ART, at a median of 1.0 month after event diagnosis, averting the “true” natural history course of their HIV infections and possibly preventing further opportunistic infections and death. The remaining portion of the cohort may not have initiated ART promptly after WHO3, WHO4, or TB events, due to reasons including antiretroviral stock outs, delays in return to clinic, concerns surrounding adherence issues, loss-to-follow-up, or reluctance from caregivers to initiate ART. We chose to censor follow-up time at ART initiation, in order to report clinical event risks among untreated children. Alternative approaches, such as competing-risk analysis,[37,38] would permit creation of survival curves and partial adjustment of clinical event risks for the impact of ART initiation over follow-up periods expanded to include time on ART, but would not permit an analysis focused only on events among children prior to ART initiation. These data thus provide an estimate of HIV disease progression in the current ART era, but prior to universal access to ART for HIV-infected infants.

The electronic databases used in this study were the product of routine clinical care in a variety of sites, rather than of a dedicated research study. As a result, they are limited in their scope and completeness. For example, we lacked information on some clinically important variables, such as prevalence and duration of breastfeeding and rates of gastroenteritis. We were also unable to record the specific diagnostic methods used for each clinical event, or to report which clinical events led to hospitalizations. However, because these data reflect clinical care, they provide great insights into the care received by children in our setting, and the large size of the database improves the applicability of our results.

This analysis makes at least two novel contributions to the existing literature. First, to our knowledge, this is the first study to simultaneously examine the impact of current CD4% and current age (see methods for definition) on incidence of WHO3, WHO4, and TB events in children less than one year of age. Second, we provide data on the rates of mortality in untreated, HIV-infected children before, immediately after, and more than 30 days after a diagnosis of WHO3, WHO4, and TB events. These data have previously been reported only

for adults.[39] The resulting trends confirm the critical importance of early HIV diagnosis among HIV-exposed infants, and support the 2010 WHO guidelines recommending ART initiation, regardless of CD4%, for all HIV-infected infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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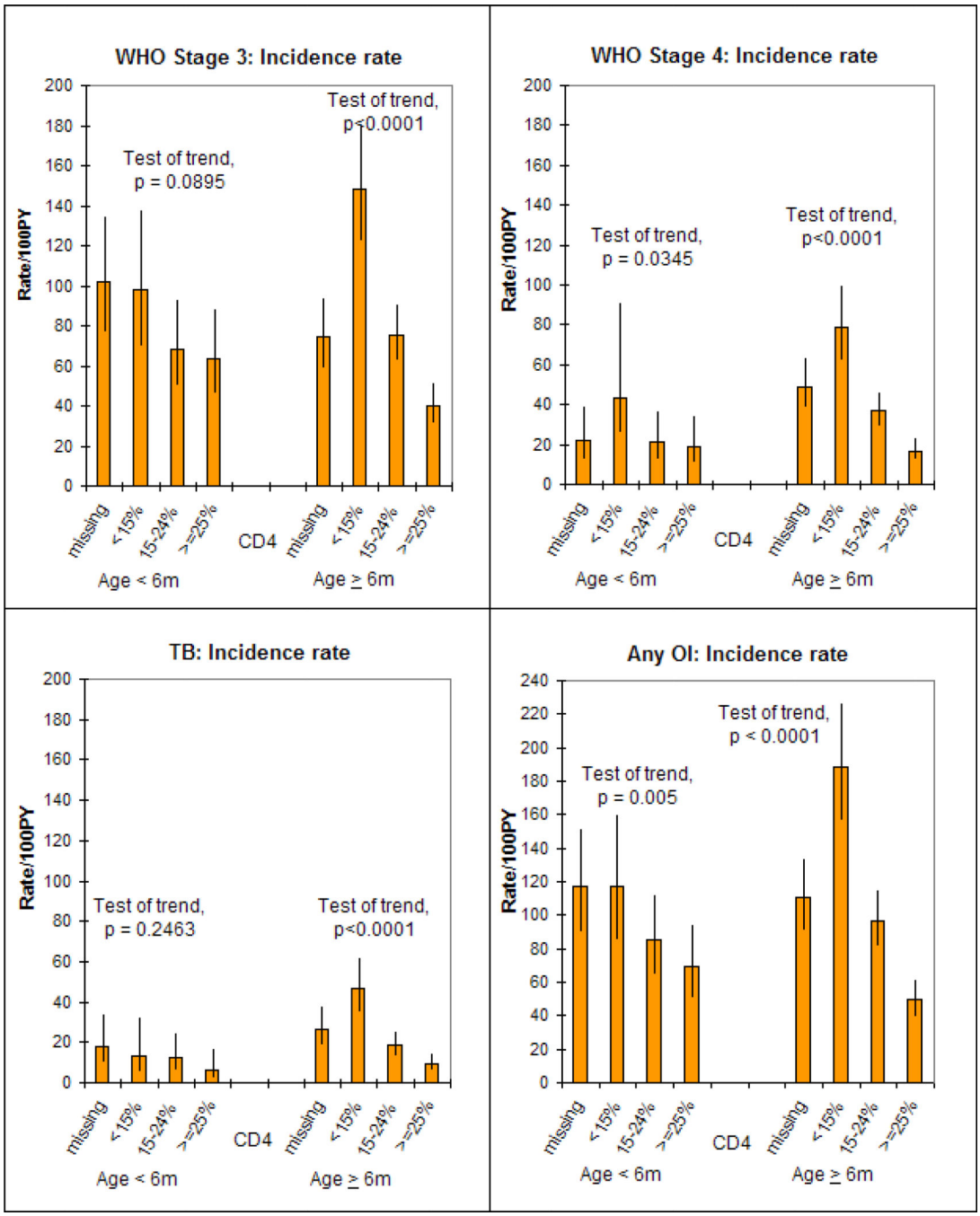

Figure 1. Incidence rates of earliest WHO Stage 3 events (except TB), earliest WHO Stage 4 events (except TB), earliest TB events, and earliest overall events prior to ART initiation among infants enrolling before 1 year of age in IeDEA East Africa

The figure depicts incidence of earliest clinical events among infants in the IeDEA East Africa cohort (full numeric results in Supplemental Table A). The vertical axis shows rates per 100 person-years. On the horizontal axis, results are shown for infants <6 months of age (left-hand group of bars in each panel) and for children ≥6 months of age (right-hand group of bars in each panel), stratified by current CD4%, as defined in Methods. A trend test of incidence rates (excluding the missing category) by CD4 stratum was performed. Incidence

rates for all evaluated events followed a statistically significant decreasing trend associated with CD4% for children aged ≥6 months; for infants aged <6 months, CD4% was only statistically significantly associated with earliest overall events and with earliest WHO4 events (p-values for test of trend analyses shown).

IeDEA: International Epidemiologic Databases to Evaluate AIDS; **WHO**: World Health Organization; **TB**: tuberculosis; **PY**: person-year; **m**: months **OI:** opportunistic infection

Table 1

Characteristics of 847 HIV-infected children enrolled in care in the IeDEA East Africa region before 1 year of age

Variable	N (%) or median (IQR)
Female	437 (51.6)
Age at enrollment (months)	4.8 (1.9–8.6)
Proportion enrolling at ≤6 months of age	482 (56.9)
Duration of follow-up before ART initiation (months) [a]	10.8 (9.7 – 12.2)
ART initiated	391 (46.2)
Death before ART initiation	75 (8.8)
Loss to follow-up before ART initiation [b]	133 (15.7)
Database closure before ART initiation	248 (29.3)
Time from enrollment to first recorded CD4 value (months) [c]	4.7 (4.2–5.5)
First recorded CD4% value	20.0% (14.0–27.0%)
<15%	170 (20.1)
15–24%	232 (27.4)
>=25%	201 (23.7)
Missing	244 (28.8)
Clinical site	
AMPATH	594 (70.1)
FACES	62 (7.3)
Morogoro	16 (1.9)
Tumbi	10 (1.2)
MTCT-Plus	165 (19.5)
Nyanza Provincial Hospital	53 (6.3)
Makerere University-Johns Hopkins University	62 (7.3)
St. Francis Hospital	50 (5.9)
Antiretroviral prophylaxis [d]	
Any maternal prophylaxis received (of 702 with data)	174 (24.8)
Any neonatal ARVs received (of 505 with data)	200 (39.6)
Neonatal regimen (of 200 receiving neonatal ARVs)	
Single-dose nevirapine	172 (86.0)
Zidovudine or zidovudine/nevirapine	19 (9.5)
Three antiretroviral drugs	2 (1.0)
Other regimen or regimen not specified	7 (3.5)
Cotrimoxazole prophylaxis (ever received)	835 (98.6)
Growth parameters at enrollment[25]	**Mean ± SD**
Length-for-age (Z-score)	−1.64±2.11
Weight-for-age (Z-score)	−1.48±1.74
Weight-for-length (Z-score)	−0.40±2.05

IQR: interquartile range; **ART**: antiretroviral therapy; **AMPATH**: Academic Model Providing Access to Healthcare; **FACES**: Family AIDS Care and Education Service: **MTCT**: mother-to-child HIV transmission; **ARVs**: antiretroviral drugs; **SD**: standard deviation.

[a] From Kaplan-Meier analysis of time from enrollment to ART initiation or child's last visit, censoring for death and loss to follow-up. Not all children in the cohort were eligible to initiate ART, per WHO and local guidelines at the time of the study.

[b] Loss to follow-up was defined as an interval of >6 months between last visit and database closure.

[c] Patients with no CD4 count were censored at the time of the start of ART or their last visit, whichever occurred first.

[d] ARV prophylaxis data were available for only a subset of patients in the database. The appropriate denominators for each variable are shown in parentheses.

Table 2

Earliest clinical events prior to ART initiation among 847 HIV-infected children enrolled in care before 1 year of age in the IeDEA East Africa region

Event	Number of children experiencing event[a]	Primary mode of diagnosis[b]	Number of events[a]	Number of events present at enrollment (% of total events)
Earliest overall events (any WHO Stage 3, WHO Stage 4, or TB event)	**613**	**n/a**	**1082**	**264 (24.4)**
Earliest WHO Stage 3 events	**520**		**585**	**182 (31.1)**
Bacterial meningitis/pneumonia/sepsis		L, C	181	65 (35.9)
Oral candidiasis		C	126	48 (38.1)
Chronic diarrhea		C	64	34 (53.1)
Moderate malnutrition		C	43	16 (37.2)
Prolonged fever		C	20	13 (65.0)
Cytopenia		L, C	7	4 (57.1)
Shingles (>2 episodes or >1 dermatome)		C	2	1 (50.0)
Lymphoid intestinal pneumonia (LIP)		R, C	1	1 (100)
Recurrent HSV stomatitis		C	1	1 (100)
Missing detailed diagnosis[c]		n/a	140	26 (18.6)
Earliest WHO Stage 4 events	**305**		**319**	**51 (16.0)**
Recurrent severe bacterial infections		R, C	121	19 (15.7)
Wasting		C	51	19 (37.3)
Pneumocystis jiroveci pneumonia		R, C	18	2 (11.1)
Esophageal candidiasis		C	15	1 (6.7)
HIV encephalopathy		C	9	1 (11.1)
Cryptococcosis		L, C	5	2 (40.0)
Kaposi's sarcoma		P, C	1	0 (0)
Chronic/visceral herpes simplex virus		C	1	0 (0)
Toxoplasmosis		R, C	1	0 (0)
Non-tuberculous mycobacterial infection		L, C	1	0 (0)
Mycobacterium avium complex (MAC)		L, C	1	0 (0)
Missing detailed diagnosis[c]		n/a	95	7 (7.4)
Earliest tuberculosis events	**171**		**178**	**31 (17.4)**
Pulmonary		L (sputum AFB smear), C	141	30 (21.3)
Extrapulmonary		L, R, P, C	14	1 (7.1)
TB site not recorded		n/a	23	0 (0)

WHO: World Health Organization; **AFB:** Acid-Fast Bacilli; **TB:** Tuberculosis.

[a]. Number of patients experiencing at least one event in each category. When children with no prior events in a given category (e.g., WHO3) event experienced multiple events in that category on the same date, we recorded the individual clinical diagnoses that comprised their first presentation in that category. Patients may have experienced multiple events at the time of their earliest event, and thus the number of events is greater than the number of children experiencing at least one event.

[b] Radiographic modalities were most often chest radiographs. L= Laboratory, C=Clinical, R=Radiographic, P=Pathologic.

[c] Missing detailed diagnosis: Patients were recorded to have experienced a WHO3 or WHO4 event, but a specific diagnosis was not recorded.

Table 3

Mortality prior to ART initiation among 847 HIV-infected infants enrolling before one year of age in the IeDEA East Africa region

Mortality Type	Rate/100PY (95% CI)
Overall mortality	7.4 (5.9 – 9.3)
Mortality with no history of WHO3, WHO4, or TB event, by current CD4%	
Missing	8.4 (3.8 – 18.7)
<15%	5.0 (0.7 – 35.4)
15–24%	4.3 (1.6 – 11.6)
≥25%	3.7 (1.6 – 9.0)
Mortality within 30 days of clinical event	
WHO3 or WHO4 event (excluding tuberculosis)	41.1 (25.5 – 66.0)
Tuberculosis	33.8 (12.7 – 90.0)
Mortality > 30 days from clinical event diagnosis	
Missing	29.1 (16.9 – 50.2)
<15%	23.0 (13.4 – 39.6)
15–24%	10.1 (5.7 – 17.8)
≥25%	4.7 (2.0 – 11.4)

PY: person-years; **CI**: confidence interval; **WHO**: World Health Organization; **WHO3**: WHO Stage 3 event; **WHO4**: WHO Stage 4 event; **ART**: antiretroviral therapy; **TB:** tuberculosis.