Impact of HIV exposure without infection on hospital course and 30-day mortality among young children in sub-Saharan Africa: a multi-site cohort study

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Abstract

Background: HIV-exposed uninfected (HEU) young children are at increased risk of hospitalization and death as compared to HIV-unexposed uninfected (HUU) children. The drivers of poor outcomes among HEU children remain unknown, limiting the development of interventions to support this vulnerable population.

Methods: We performed a secondary analysis of data from a large multi-country prospective cohort Childhood Acute Illness and Nutrition (CHAIN) Network study. Hospitalized children aged 2-23 months were followed from an index admission for 6 months after discharge to determine acute and long-term outcomes. Data from the 5 sites in Uganda, Kenya, and Malawi were included. Using perinatal HIV exposure (HEU and HUU) as the primary exposure and adjusting for child, caregiver, and household characteristics, we compared 30-day survival outcomes, nutritional status, illness severity, and utilization of inpatient resources.

Results: We included 1486 children: 217 HEU and 1269 HUU. Wasting and stunting were more frequent in HEU than HUU children, with adjusted OR 1.46, 95% CI (1.06-2.01) and adjusted OR 2.03, 95% CI (1.42 – 2.90), respectively. HEU children were twice as likely to have a prolonged hospital stay compared to HUU children [adjusted OR 2.17, 95% CI (1.23- 3.80)], despite no significant difference in the prevalence of severe illness at admission [adjusted OR 1.25, 95% CI (0.88-1.77)]. Admission diagnoses and use of inpatient resources also did not differ significantly between groups. HEU children had an increased risk of mortality during the 30 days following hospital admission [adjusted hazard ratio 1.75, 95% CI (1.09-2.80)].

Conclusions: HEU childrenare more likely to be wasted and stunted, have prolonged hospital stay, and die within 30 days of hospitalization, as compared to HUU children. Hospitals in settings where maternal HIV infection remains common should ensure that maternal HIV status is established among children requiring admission and build capacity to provide additional hospital monitoring and early post-discharge support for HEU children.

BACKGROUND

Successful prevention of mother-to-child transmission (PMTCT) of HIV infection has led to a dramatic decrease in the number of children with perinatally acquired HIV infection worldwide [1]. Given the persistently high prevalence of HIV infection among women of childbearing age in some populations, there has been a subsequent increase in children who are HIV-exposed but uninfected (HEU) [2]. In 2022, there were an estimated 15.4 million HEU children, with close to 90% residing in Sub-Saharan Africa [3]. Five countries account for over 50% of HEU children, including South Africa (23.8%), Uganda (7.5%), Mozambique (6.6%), Tanzania (6.1%), and Nigeria (6.0%) [4].

HEU children, particularly in the first 2 years of life, are more vulnerable to poor health outcomes [5, 6] as compared to HIV-unexposed-uninfected (HUU) children. Studies performed both prior to and following

widespread access to antiretroviral therapy (ART), demonstrate that HEU children are at higher risk of mortality compared to HUU children [7–10]. The vulnerability of HEU children is not restricted to low-and-middle-income countries (LMIC), but is also seen in better-resourced settings such as the United States [11]. However, drivers of morbidity and mortality among HEU children remain unclear, a knowledge gap that hampers efforts to improve outcomes. Currently, there are limited international guidelines to support provision of additional resources to this vulnerable and growing population of children.

Multiple unique exposures and immunologic abnormalities have been described among HEU children during the first years of life that may predispose to morbidities and death [12–14]. These include intrauterine and postnatal exposure to ART, intrauterine and postnatal exposure to chronic viral infections (in additional to HIV) such as CMV, maternal dysbiosis and metabolic derangements impacting fetal and post-natal immune development, reduced duration of breastfeeding, and compromised transfer of protective maternal antibodies during gestation and breastfeeding. Additionally, HEU children are at increased risk of *Mycobacterium tuberculosis* infection which may contribute to poor growth and early mortality [5]. There is also evidence that universal risk factors for early childhood morbidity, including poor birth outcomes (preterm birth and low birth weight), suboptimal breastfeeding, and maternal mortality and poverty, occur more frequently in HEU children compared to HUU children [12–15]. The social and economic impact of living-with-HIV on families may also influence childhood health outcomes. For example, parents-living-with-HIV may experience more episodes of illness and visits to medical providers that have significant economic impact. An income earning partner may not be able to work or may experience premature death. Mothers-living-with-HIV may be at risk for increased psychological stress, depression and stigmatization [16] that negatively impact their capacity to care for their children and place households at increased risk for malnutrition and illness [17].

There have been limited studies that examine risk factors for poor outcomes during hospitalization among HEU children, as compared to those who are HUU. For example, nutritional status has long been recognized as key to healthy childhood growth, neurodevelopment, and survival during severe illness [18, 19]. Undernutrition puts children at greater risk of dying from common infections, increases the frequency and severity of such infections, and delays recovery [20]. The impact of HIV-exposure on early childhood nutritional status and mortality risk remains unclear [7, 9], and could be mediated by both biologic and social influences. Illness severity is directly related to mortality and prolonged hospitalization that may put surviving children at risk of nosocomial infections, colonization with resistant pathogens, and is also associated with increased costs to the family. We explored the associations between HIV exposure without HIV infection and 30-day mortality, nutritional status, illness severity, utilization of hospital resources and hospital length of stay among young children hospitalized in Kenya, Uganda, and Malawi.

METHODS

Study design and participants:

Here we present a secondary analysis of data collected during the Childhood Acute Illness and Nutrition (CHAIN) cohort study. The CHAIN study enrolled children 2 to 23 months old at the time of admission to hospital for any acute illness (excluding trauma, poisoning, and complications of congenital defects), at nine sites across Sub-Saharan Africa and South East Asia, between November 2016 and January 2019 [21]. In this analysis, we analyzed data from five CHAIN sites with high prevalence of maternal HIV infection: Kampala (Uganda), Blantyre (Malawi), Migori (Kenya), Mbagathi (Nairobi, Kenya) and Kilifi (Kenya). To ensure representation of all nutritional status, children were recruited in three strata of no wasting, moderate wasting and severe wasting/kwashiorkor (nutritional edema) in ratio 2:1:2. Details of the CHAIN cohort study have been previously published [21]. In brief, children were followed daily from hospital admission through discharge, and then at scheduled follow-up assessments 45-, 90-, and 180-days following hospital discharge. For this secondary analysis, data collected from hospital admission through discharge and up to 30 days from the date of admission were included. Both inpatient mortality and deaths within 30 days from hospital admission (to capture deaths that occurred during the early post-discharge period) were examined.

HIV testing and classifications:

All children and their mothers underwent rapid diagnostic testing for HIV infection at study enrollment using either the Alere 2, Determine HIV 1/2, or Uni-gold HIV 1/2, rapid tests. Manufacturer recommended standard operating procedures were followed. The rapid test was repeated to confirm a positive result, and/or if the results were invalid. Children with positive rapid tests, and all children < 18 months old born to mothers-living-with-HIV, had HIV DNA-PCR confirmatory testing performed. A child was considered HUU if both child and maternal HIV rapid test results were negative. A child was considered HEU if their mother was known to be living-with-HIV while pregnant and the child's confirmatory HIV test was negative, and/or a child < 18 months old had positive HIV rapid tests and the child's confirmatory HIV DNA-PCR test was negative. Children with positive HIV rapid tests and positive HIV DNA-PCR were considered HIV-infected. If a child's mother was not available for HIV-testing, HIV-exposure could be confirmed by verbal report from a caregiver that the child's mother was known to be HIV-infected during pregnancy. Only HEU and HUU children were included in this secondary analysis. Children with confirmed HIV, and children with unknown HIV infection or exposure status, were excluded.

Anthropometric Assessments:

Anthropometry (weight, length, mid-upper-arm-circumference/MUAC) was assessed at admission and discharge. Measurements were performed by two trained study staff following standardized protocols and using calibrated scales, length boards, and MUAC tapes provided by UNICEF. Nutritional status was determined by MUAC, using the following definitions: not wasted, MUAC ≥ 12.5cm (age ≥ 6 months) or MUAC ≥ 12cm (age < 6 months); moderate wasting, MUAC 11.5 to < 12.5cm (age ≥ 6months) or MUAC 11 to < 12cm (age < 6 months); severe wasting or kwashiorkor, MUAC < 11.5cm (age ≥ 6 months) or MUAC < 11cm (age < 6 months) or bilateral pedal oedema not explained by other medical causes. For this specific analysis, nutritional status is reported as wasting and stunting. For wasting, two nutritional categories were created: 1) not wasted, MUAC ≥ 12.5cm (age ≥ 6 months) or MUAC ≥ 12cm (age < 6 months); 2)

wasted, MUAC < 12.5cm (age ≥ 6 months) or MUAC < 12cm (age < 6 months) or bilateral pedal oedema not explained by other medical causes. Stunting was defined as a height for age Z score < -2 standard deviations from the WHO child growth standards median.

Data collection, clinical, and socioeconomic variables:

Detailed clinical data were prospectively collected at hospital admission; social and demographic data were collected within the next 48 hours using standardized tools. Admission diagnosis(es) was recorded, as was receipt of medications such as antibiotics and/or traditional medications prior to presentation. As previously reported, an illness severity score was assigned to each child at hospital admission based on the presence of features of systemic inflammatory response syndrome (SIRS) [22]. The four criteria included: heart rate low (< 90) or high (> 180)/min; axillary temperature low (< 36^0C) or high (≥ 38.5^0C); respiratory rate high (> 34 breaths per minute) and WBC low (< 5 x10^9/L) or high (> 17.5 x10^9/L) [23]. Illness severity scores ranged from 0–4 (0 = none, 1 = one sign, 2 = two signs, 3 = three signs, 4 = all the four signs). Subsequently, illness severity was collapsed into a binary variable [23]: none or one sign (low illness severity) versus two or more signs (high illness severity).

All enrolled children were assessed daily throughout their hospitalization to assess signs of clinical progress or deterioration, such as presence of WHO danger signs [24], and to monitor use of inpatient resources including supplemental oxygen, feeding tubes, and second line antibiotics. Length of hospital stay was computed by obtaining the number of days from admission to discharge or death. Dates, times, and presumed causes of inpatient deaths were collected from medical files and healthcare providers. For children who left hospital against medical advice prior to discharge, length of stay was computed by obtaining the number of days from admission to the date they left hospital. In addition to deaths occurring while inpatient, deaths that occurred post-discharge but within 30 days of admission to hospital were also captured (30-day mortality) through verbal contact with parent or guardian, and/or review of hospital records for children who died during a re-admission [10].

Demographic and socioeconomic data included: vital status of child's biological mother, caregiver age, weight and height, and education level. Standardized questionnaires were used to assess household food security and wealth index. A set of eight questions from the Food Insecurity Experience Scale (FIES) was adapted and asked to caregivers to assess household food insecurity [10]. A categorical variable defining food insecurity was created with a score of 0–3, 4–6 and 7–8 defined as low, moderate and severe food insecurity, respectively. Appropriate diet variable was defined as: exclusively breastfed for children < 6 months, more than or equal to two food groups and breastmilk for children 6 to 9 months, and more than or equal to four food groups plus breastmilk for children 10 to 23. Assessment of household ownership of assets such as a television or bicycle, and housing structure were adapted from the Demographic and Health Survey (DHS). Assets and housing structure variables were then used to derive the household asset index using principal component analysis (PCA). Variables with the percentage of missing data less than 10% were imputed using the iterative PCA method before running PCA on complete

observations. Asset quintiles were expressed in terms of quintiles with five categories depicting from the poorest to the least poor with each category representing approximately 20% of the participants.

All data were recorded in paper case report forms by trained staff, reviewed by site study coordinators prior to entry into a Research Electronic Data Capture (REDCap) database, and underwent validation checks by the CHAIN network data management team.

Statistical Analysis

All available data from hospitalized HEU and HUU children at the Ugandan, Kenyan, and Malawi CHAIN sites were included, and children documented to be infected with HIV were excluded. *A priori* power calculations were not performed. The main exposure variable considered was perinatal HIV exposure, with analysis focusing on HEU and HUU children. The study outcomes were inpatient mortality, 30-day mortality, nutritional status at admission, illness severity at admission, hospital length of stay, and utilization of inpatient resources. All the analyses are weighted to reflect the stratification by nutritional status using inverse weights (1, 0.40, 0.39 for the not wasted, moderately wasted, and severely wasted and/or kwashiorkor) as explained elsewhere [10]. Children's characteristics at the time of admission and discharge from hospital stratified by HIV exposure category (HEU and HUU) are reported.

For inpatient mortality, days to death between the HIV exposure groups were compared using Wilcoxon Rank Sum test. To assess the effect of HIV exposure on inpatient mortality, a logistic regression model adjusting for nutritional status (wasted vs non-wasted enrolment strata), sampling inverse weights and recruiting hospital was used. For the 30-day mortality after hospital admission, multilevel parametric survival regression model with a Weibull probability distribution (as previously reported) [10] adjusting for sex, age, nutritional status, sampling inverse weights and site as random intercept was conducted to assess effect of HIV exposure on mortality.

To assess the relationship between HIV exposure and nutritional status (binary wasted vs not wasted, and stunted vs not stunted) at hospitalization, logistic regression models were used. The models were adjusted for child's age and sex *a priori*, inverse sampling weights, hospital travel time, prematurity at birth, household food insecurity, household assets, whether the primary caregiver was the biological mother, and recruiting site.

To assess the relationship between HIV exposure and illness severity (binary low and high), logistic regression model was used adjusted for child's age, breastfeeding and sex *a priori*, inverse sampling weights and recruiting site.

To assess the relationship between HIV exposure and duration of hospitalization, duration of hospitalization was categorized into binary variable using the median length of hospital stay (5 days) as the cut-off: short and long duration of hospital stay. Length of hospital stay analysis was restricted to survivors and also excluded those who left against medical advice or absconded. We hypothesized that nutrition status could modify the length of hospitalization and formally tested for effect modification using the Breslow Day test of homogeneity. This analysis used logistic regression adjusted for *a priori*:

illness severity score, food insecurity, inverse sampling weights, recruiting site and the interaction term with nutrition status.

To assess the effect of HIV exposure on occurrence of daily danger signs and resource utilization (oxygen use, nasogastric tube use, and antibiotic switch), days with any danger sign or the use of a specific resource were counted. A zero-inflated negative binomial regression model was applied because the days with a danger sign or using any of the resources had leading zeros and was over dispersed. The zero-inflated negative binomial regression was conducted for danger sign and each resource separately and adjusted for site, inverse weights and prior confounders (age, sex). The reported measure of effect was incident rate ratio and corresponding 95% confidence intervals (95%CI)

We defined switching of antibiotics as a binary variable reflecting change from the first-line medication (intravenous ampicillin/benzylpenicillin and gentamicin) to a second-line or third-line intravenous antibiotic (cephalosporins, fluoroquinolones, carbapenems, and amphenicols). We compared the occurrence of antibiotic switch between the HIV exposure groups (HEU and HUU) using the chi-square test.

All statistical analyses were conducted using STATA College Station TX version 15.0 and the level of significance was assessed using two-tailed $\alpha < 0.05$ or 95% CIs.

Ethical considerations:

Ethical approval

was obtained from the Oxford Tropical Research Ethics Committee, and each site-specific institutional review board: Scientific & Ethical Review Unit (SERU), Kenya Medical Research Institute in Kenya; Makerere University School of Biomedical Sciences Research Ethics Committee in Uganda; and COMREC, Kamuzu University of Health Sciences in Malawi. Written, informed consent was obtained from caregivers of all study participants in their preferred local language.

RESULTS

Description of study participants

Out of the 3101 hospitalized children in the CHAIN cohort study from all sites, 1488 participants from the Asian sites (Bangladesh, Karachi) and Burkina Faso were excluded from this analysis (Figure 1). Further, 26 participants with unknown HIV status and 101 children-living-with-HIV were excluded. Thus, 1468 children were included in this analysis: 1269 HUU and 217 HEU children.

Figure 1: Flow diagram demonstrating children included in analysis.

Baseline characteristics of hospitalized children

Tables 1-2 illustrate the baseline characteristics of participating children and their caregivers. Overall, 55.3% of the participants were male and the median age was 11.2 months. Only 7% of children were reported as born prematurely, 7% did not have their biological mother as the primary caregiver, and 3% of biologic mothers were reported as deceased. Sixty-seven percent of all children were breastfeeding at admission to hospital. Over half of mothers were 25-50 years of age, and over half had attained primary level as their highest level of education. The Kampala site contributed the most children to the study population.

Sex, child's age group, birth weight, and caregiver's education level were comparable between HIV exposure categories. HEU children were more likely to be wasted and stunted, less likely to be breastfeeding, and less likely to be receiving an age-appropriate diet as compared to HUU children. Forty-seven percent of HUU children had a low food insecurity score, with 17% reporting high food insecurity. In comparison, the highest proportion of HEU children (41%) had moderate score of food insecurity, with 27% reporting high food insecurity. Household assets were also significantly different between families with HEU versus HUU children, with HEU children less likely to come from the least poor households.

Table 1

Table 1: Child demographic and clinical characteristics at the time of hospital admission categorized by HIV exposure group.

Characteristic	HUU	HEU	Total	P-value
Sex				
Male	705 (55.6)	117 (53.9)	822 (55.3)	0.654
Female	564 (44.4)	100 (46.1)	664 (44.7)	
Age group				
12 & above	581 (45.8)	97 (44.7)	678 (45.6)	0.875
6 to 11	472 (37.2)	80 (36.9)	552 (37.2)	
<6months	216 (17.0)	40 (18.4)	256 (17.2)	
Site				
Kilifi	217 (17.1)	12 (5.53)	229 (15.4)	< 0.001
Mbagathi	244 (19.2)	27 (12.4)	271 (18.2)	
Migori	198 (15.6)	56 (25.8)	254 (17.1)	
Kampala	387 (30.5)	59 (27.2)	446 (30.0)	
Blantyre	223 (17.6)	63 (29.0)	286 (19.3)	
Birth weight				
Median (IQR)	3.1 (0.90)	3.2 (0.90)	3.1 (0.90)	0.698
Mean (SD)	3.1 (0.75)	3.1 (0.68)	3.1 (0.74)	
Born premature				
No	1178 (92.8)	208 (95.9)	1386 (93.3)	0.1
Yes	91 (7.2)	9 (4.2)	100 (6.7)	
Breastfeeding (any)				
No	373 (29.4)	113 (52.1)	486 (32.7)	<0.001
Yes	896 (70.6)	104 (47.9)	1000 (67.3)	
Appropriate diet (all)				
No	668 (52.6)	153 (70.5)	821 (55.2)	<0.001
Yes	601 (47.4)	64 (29.5)	665 (44.8)	
Age				
< 6 months				
No	121 (56.0)	28 (70)	149 (58.2)	0.1

Yes	95 (44.0)	12 (30)	107 (41.8)	
6-9 months				
No	107 (34.7)	27 (46.6)	134 (36.6)	0.087
Yes	201 (65.3)	31 (53.4)	232 (63.4)	
10-23 months				
No	440 (59.1)	98 (82.4)	538 (62.3)	<0.001
Yes	305 (40.9)	21 (17.6)	326 (37.7)	
Wasting				
Wasting	747 (58.9)	140 (64.5)	887 (59.7)	0.117
No wasting	522 (41.1)	77 (35.5)	599 (40.3)	
Stunting				
No	668 (52.8)	83 (38.2)	751 (50.7)	<0.001
Yes	596 (47.2)	134 (61.8)	730 (49.3)	
Used traditional medicine in last 7 days				
Yes	75 (5.9)	15 (6.9)	90 (6.1)	0.567
Used antibiotics in last 7 days				
Yes	516 (40.7)	88 (40.5)	604 (40.6)	0.976
Diagnosis of pneumonia at admission				
Yes	500 (39.4)	78 (35.9)	578 (38.9)	0.334
Diagnosis of gastroenteritis at admission				
Yes	436 (34.4)	82 (37.8)	518 (34.9)	0.327
Diagnosis of sepsis at admission				
Yes	264 (20.8)	47 (21.7)	311 (20.9)	0.775
Diagnosis of malaria at admission				
Yes	188 (14.8)	32 (14.7)	220 (14.8)	0.979
High illness severity at admission				
Yes	474 (37.4)	83 (38.3)	557 (37.5)	0.801

Data presented as n (%), mean (SD), median (IQR), n-frequency;

Appropriate diet variable was defined as: exclusively breastfed for children <6 months, more than or equal to two food groups and breastmilk for children 6 to 9 months and more than or equal to four food groups plus breastmilk for children 10 to 23 months.[10]

Table 2: Caregiver and household characteristics at the time of hospital admission, categorized by HIV exposure group.

Characteristic	HUU	HEU	Total	p-value
Caregiver age				
<18	41(3.2)	9 (4.2)	50 (3.4)	0.638
18 to 50	1209 (95.3)	206 (94.9)	1415 (95.2)	
>50	19 (1.5)	2 (0.9)	21 (1.4)	
Caregiver BMI				
Underweight	83 (6.5)	23 (10.6)	106 (7.1)	0.02
Normal	796 (62.7)	144 (66.4)	940 (63.3)	
Overweight & Obese	390 (30.7)	50 (23.0)	440 (29.6)	
Caregiver education level				
Secondary/above	544 (42.9)	88 (40.6)	632 (42.5)	0.811
Primary	644 (50.8)	115 (53.0)	759 (51.1)	
None	81 (6.4)	14 (6.4)	95 (6.4)	
Biological Mother alive				
Yes	1228 (96.8)	210 (96.8)	1438 (96.8)	0.997
No	41 (3.2)	7 (3.2)	48 (3.2)	
Hospital travel time				
<1 hr	542 (44.0)	105 (49.1)	647 (44.7)	0.284
1-2 hrs	523 (42.4)	82 (38.3)	605 (41.8)	
>2 hrs	168 (13.6)	27 (12.6)	195 (13.5)	
Food insecurity				
Low	598 (47.1)	71 (32.7)	669 (45.0)	< 0.001
Moderate	455 (35.9)	89 (41.0)	544 (36.6)	
High	216 (17.0)	57 (26.3)	273 (18.4)	
Household assets				
Poorest	311 (24.5)	55 (25.4)	366 (24.6)	0.026
Second	221 (17.4)	54 (24.9)	275 (18.5)	
Middle	317 (25.0)	53 (24.4)	370 (24.9)	
Fourth	278 (21.9)	42 (19.4)	320 (21.5)	

Least poor	142 (11.2)	13 (6.0)	155 (10.4)

Data presented as n (%), n-frequency; Abbreviations: HUU- HIV unexposed uninfected, HEU- HIV exposed uninfected, BMI- Body mass index

HIV exposure and mortality

Among HEU and HUU children, 24/217 (11.1%) and 77/1269 (6.1%) died, respectively, during hospitalization. Time-to-death was not significantly different, with a median number of 3 days among HUU and 4 days among HEU children (p=0.23). In the multivariable model, the effect of HIV exposure on inpatient mortality was borderline, adjusted Odds Ratio (aOR) 1.61 (95%CI 0.97-2.67). Within 30 days following hospital admission, 29/217 (13.4%) and 90/1269 (7.1%) deaths occurred among the HEU and HUU children, respectively. In the multivariable model, HIV exposure was associated with almost double hazard of 30-days mortality: aHR 1.75 (CI -1.09-2.80, p=0.021; Figure 2)

Figure 2: Kaplan-Meier survival curve showing survival rate versus number of days following hospital admission

Abbreviations: HUU-HIV unexposed uninfected, HEU- HIV exposed uninfected; Logrank test for equality of survivor functions, p = 0.0004

HIV exposure and nutritional status

In the univariable model, HIV exposure was associated with stunting but not wasting. However, in the multivariable adjusted model, HEU children demonstrated nearly 50% higher odds of being wasted (aOR 1.46 [95% CI 1.06—2.01]; Table 3, Supplemental table 1) and a two-fold odds of being stunted at admission to hospital (aOR 2.03(95% CI 1.42 – 2.90; Table 3).

HIV exposure, illness severity, admission diagnosis, and presence of clinical danger signs

A high illness severity score was not associated with HEU in unadjusted (OR 1.02, CI 0.74-1.42) or adjusted (OR 1.25, CI 0.88-1.77, p=0.22; Supplemental table 2) models. Admission diagnosis did not differ between HEU and HUU children (Table 1). There were no significant differences in the frequency and types of danger signs reported between HEU and HUU children (Supplemental table 3).

HIV exposure, duration of hospitalization, and use of inpatient resources

In the unadjusted model, the odds of having a prolonged (>5 days) hospital stay among the HEU children was not significantly different from HUU children (Table 3). After adjusting for food insecurity, enrollment site, illness severity at admission and nutritional status (wasted/non-wasted), the odds of prolonged hospitalization among HEU children were more than twice as much as that observed for HUU children (Supplemental table 4). In a stratified analysis based on nutritional status (wasted/non-wasted), the odds of a prolonged hospital stay were more than twice in non-wasted HEU versus HUU children. We also compared the use of inpatient resources (specifically: supplemental oxygen, nasogastric tube placement, and switch to second line antibiotics) between HEU and HUU children. There were no significant differences in the requirement for use of inpatient resources between HEU and HUU children. (Supplemental Tables 5 and 6).

Table 3: Summary of odds ratios of wasting and stunting at admission and having a prolonged hospitalization by HIV-exposure

Wasting/stunting at admission						
Unadjusted model				**Adjusted model**		
Exposure	Odds ratio	CI	P-value	Odds ratio	CI	P-value
HUU	Ref	-	-	Ref	-	-
HEU[¥]	1.27	0.94-1.71	0.120	1.46	1.06-2.01	0.022
HEU[β]	1.75	1.27-2.41	0.001	2.03	1.27 – 2.41	<0.001
Prolonged length of hospital stay						
Unadjusted model				**Adjusted model**		
Exposure	Odds ratio	CI	P-value	Odds ratio	CI	P-value
HUU	Ref	-	-	Ref	-	-
HEU	1.33	0.94-1.89	0.101	2.17	1.23-3.80	0.007
HEU-non wasted[£]	1.81	1.00-3.25	0.048	2.63	1.43-4.84	0.002
HEU-wasted[α]	0.93	0.61-1.41	0.724	0.97	0.62-1.52	0.898

HUU-HIV unexposed uninfected, HEU- HIV exposed uninfected. [¥]Odds ratio of wasting by HIV exposure category; [β]odds ratio of stunting by HIV exposure category. [£]Odds ratios, confidence intervals and corresponding p values for non-wasted children. [α]Odds ratios, confidence intervals and corresponding p values for wasted children.

DISCUSSION

The effective implementation of PMTCT programs to limit perinatal HIV transmission represents one of the most important public health interventions to promote early childhood survival, particularly in parts of sub-Saharan Africa where HIV-infection remains prevalent in women of childbearing age. Over the past two decades, however, HEU young children have emerged as an expanding vulnerable population that experiences increased mortality and morbidities, in both limited and well-resourced settings [7, 8, 10, 11, 25]. This analysis explored associations between HIV-exposure-without-infection and in-patient and 30-day mortality, as well as multiple clinical and sociodemographic characteristics, to provide insight into drivers of poor outcomes among hospitalized HEU young children. Confirming prior reports, a significantly increased risk of 30-day mortality was found among HEU, as compared to HUU, children [10]. HEU children were more likely to be wasted and stunted at hospital admission, and their households reported greater food insecurity and fewer economic resources. Although HEU children were more likely to require a prolonged hospital stay, unexpectedly, prolonged hospitalization was not observed when comparing wasted HIV-exposed versus wasted HIV-unexposed children. Rather, hospitalization was prolonged among non-wasted HEU children as compared to non-wasted HUU children. We did not detect significant differences in illness severity, admission diagnosis, the presence of clinical danger signs, or an increased requirement for inpatient resources among HEU children to explain their increased mortality or hospital length-of-stay. We can conclude that young, hospitalized, HEU children represent a distinct population with increased vulnerability to wasting and stunting, prolonged hospitalization, and death within 30 days of hospitalization.

Malnutrition, specifically severe wasting, is a well-recognized risk factor for early childhood mortality and morbidities [26, 27]. In this analysis, HEU children experienced significantly higher 30-day mortality rates, and their hazard of death remained elevated when accounting for nutritional status. Thus, we cannot attribute the increased 30-day mortality to poor nutritional status alone for this cohort of HEU children. Together these findings support that HEU children under 2 years of age are uniquely vulnerable to dying during hospitalization and the early post-discharge period, regardless of nutritional status.

Although malnutrition has been associated with pediatric HIV-infection [28], the association between malnutrition and HIV-exposure among HEU children remains controversial [26-28]. HEU children may be more vulnerable to undernutrition due to the reduced prevalence of breastfeeding in this population, as well as the economic effects of HIV-infection on the caregiver and/or household that may limit access to age-appropriate complimentary foods. In our study, households of HEU children were more likely to report high food insecurity and to have fewer household assets. However, we carefully assessed for confounding between HIV exposure and sociodemographic factors and subsequently adjusted for covariates including sex, age, travel time to the hospital, household food insecurity, assets, and mother as primary caregiver. We hypothesize that feeding practices (particularly limited breastfeeding) were the primary driver of poor nutritional status among HEU children in this study [29]. Additional biological factors that we were unable to quantify in our analysis, such as intestinal dysbiosis, metabolic derangements, and/or subclinical infections such as cytomegalovirus, could have also contributed to wasting [30-33] and the poor outcomes observed among HEU children.

Despite the increase in 30-day mortality, there was no significant difference in illness severity at admission between HEU and HUU children. Our findings contrast to those reported in South Africa, where HEU children in the community had a 4 times greater odds of experiencing a very severe infection when compared to HUU children [14]. The frequencies and types of danger signs also did not differ between HEU and HUU children. It is possible that the higher prevalence of wasting among HEU children in our study population masked typical clinical signs of sepsis, as has been reported among severely wasted HUU children [34]. We did observe a significantly higher odds of prolonged hospital stay among HEU children following adjustment for nutritional status, suggesting that non-wasted HEU children require additional time and support to recover as compared to non-wasted HUU children. Although prolonged hospitalization has been previously reported among HEU children [14], the drivers of prolonged stay among the non-wasted HEU population remain unclear. We did not observe differences in age, prematurity, or illness severity between our HEU and HUU populations. We also did not detect significant differences in the need for hospital resources between HEU and HUU children. However, the presence of sub-clinical infection or acquisition of nosocomial infection may have been more likely to complicate recovery among HEU children. Prolonged hospitalization not only places HEU children at increased risk for hospital-acquired infection and emergence of antimicrobial resistance, but also increases the financial burden to the family. Our findings suggest that HEU children should be considered a high risk population during hospitalization and in the early post-discharge period, regardless of perceived illness severity and nutritional status at admission.

The study has several strengths. Firstly, this is a large multisite study involving both rural and urban African sites making the findings generalizable across high-burden HIV-settings in sub-Saharan Africa. Secondly, comprehensive, and relevant data were systematically collected that encompassed child, caregiver, and household characteristics, so that covariates could be considered in our statistical approaches. Thirdly, this is one of the few studies to examine both inpatient and 30-day mortality in young, African children. Finally, the study also included detailed data on nutritional status, illness severity, length-of-stay, and daily use of hospital resources, between HEU and HUU children. However, the study also had several limitations. One of the limitations to this analysis is that for the nutritional status and illness severity as outcomes, the design was cross-sectional and therefore temporal relationships between variables cannot be ascertained. Secondly maternal clinical and immunological variables, such as use of highly active antiretroviral therapy, CD4 count, and HIV viral load were not collected in the study which could have an effect on study outcomes. Finally, as an observational study we cannot assume that our findings are free from confounding despite our extensive efforts to control for these factors in the analysis.

Our findings have a number of implications for future research. Longitudinal studies, preferably beginning in pregnancy, are likely to be required to understand how perinatal HIV-exposure in the absence of infection compromises early childhood health. Identifying biologic drivers of increased hospital mortality, wasting, and prolonged hospitalization among HEU children is essential to develop clinical care guidelines tailored to support this unique and vulnerable population.

CONCLUSION

Young children who are HIV-exposed but uninfected are more likely to present to hospital wasted and stunted. Following admission, young HEU children are at increased risk of death within 30 days of hospitalization and to require a prolonged hospitalization; these specific risks appear independent of admission nutritional status and are not evident from signs of clinical severity.

RECOMMENDATIONS

Public health programs and hospital systems serving populations with a high prevalence of HIV-infection among women of childbearing age need to ensure that HIV-exposure status is established among HIV-uninfected children requiring hospitalization by testing both mothers and children. Hospitalized HEU young children should be managed as a population with increased vulnerability to death within 30 days of admission and be prioritized for additional support and post-discharge assessments to monitor recovery. Research that delineates the biologic mechanisms driving poor outcomes among HEU children is needed to develop effective strategies that improve survival and shape clinical care guidelines for this growing population of vulnerable children.

Abbreviations

AIDS: Acquired immunodeficiency syndrome

ART: Antiretroviral Therapy

CHAIN: Childhood Illness and Nutrition Network

CI: Confidence Interval

CRF: Case Report Form

DNA: Deoxyribonucleic acid

HIV: Human Immunodeficiency Virus

IRB: Institutional Review Board

OR: Odds ratio

PCR: Polymerase Chain Reaction

PMTCT: Prevention of mother to child transmission

SIRS: Systemic Inflammatory response syndrome

SSA: Sub-Saharan Africa

UNICEF: United Nations Children's Fund

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

The ethical approval of the parent study was obtained from the Oxford Tropical Research Ethics Committee and ethics committees of all participating institutions. Written consent was obtained from caregivers of all study participants for current and future use of study data and samples

Consent for publication: Not Applicable

Availability of data and materials:

The CHAIN cohort data and analysis code are deposited and may be requested at: https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/5H5X0P.

Competing interests: The authors declare that they have no competing interests

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Figures

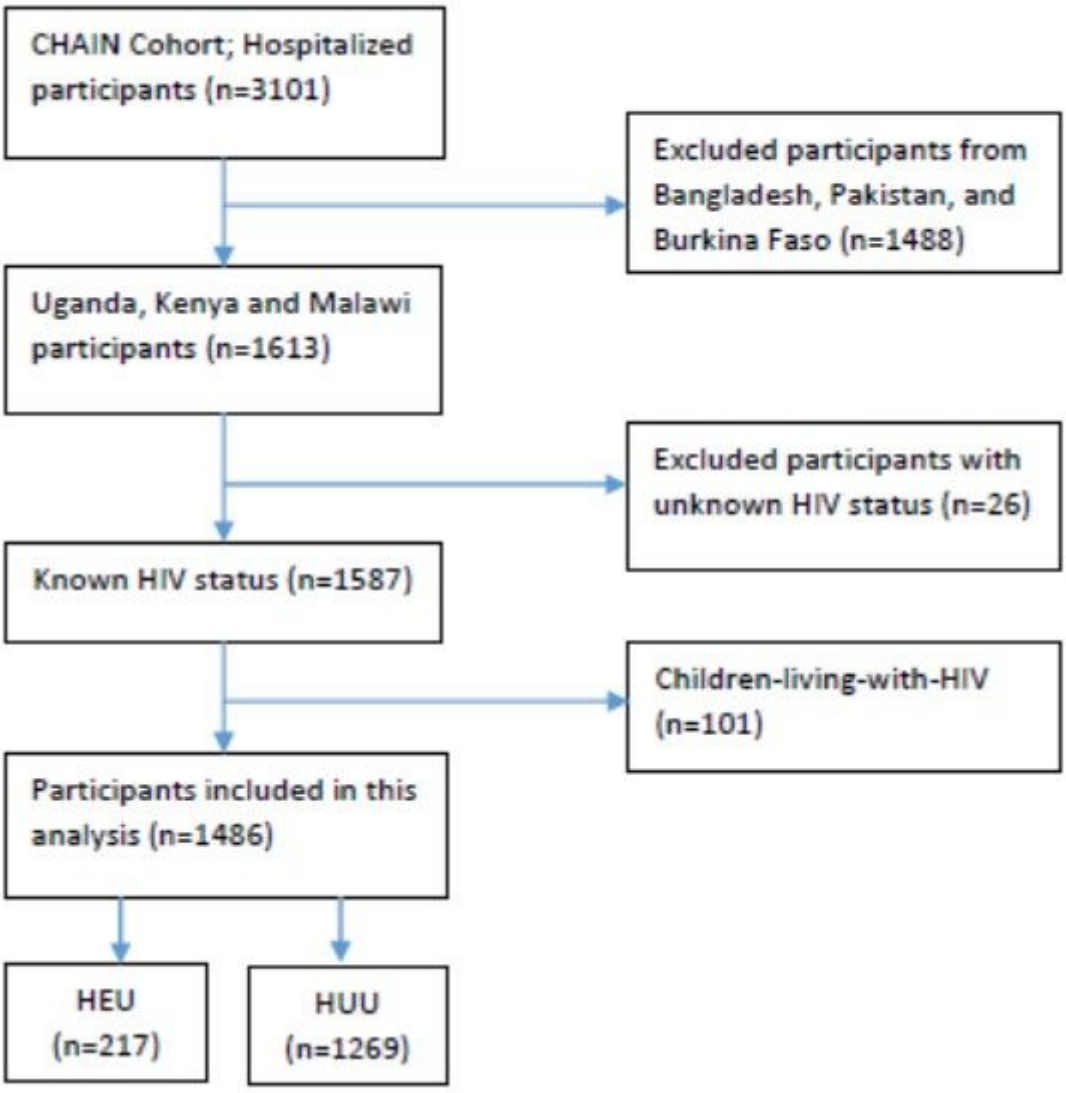

Figure 1

Flow diagram demonstrating children included in analysis.

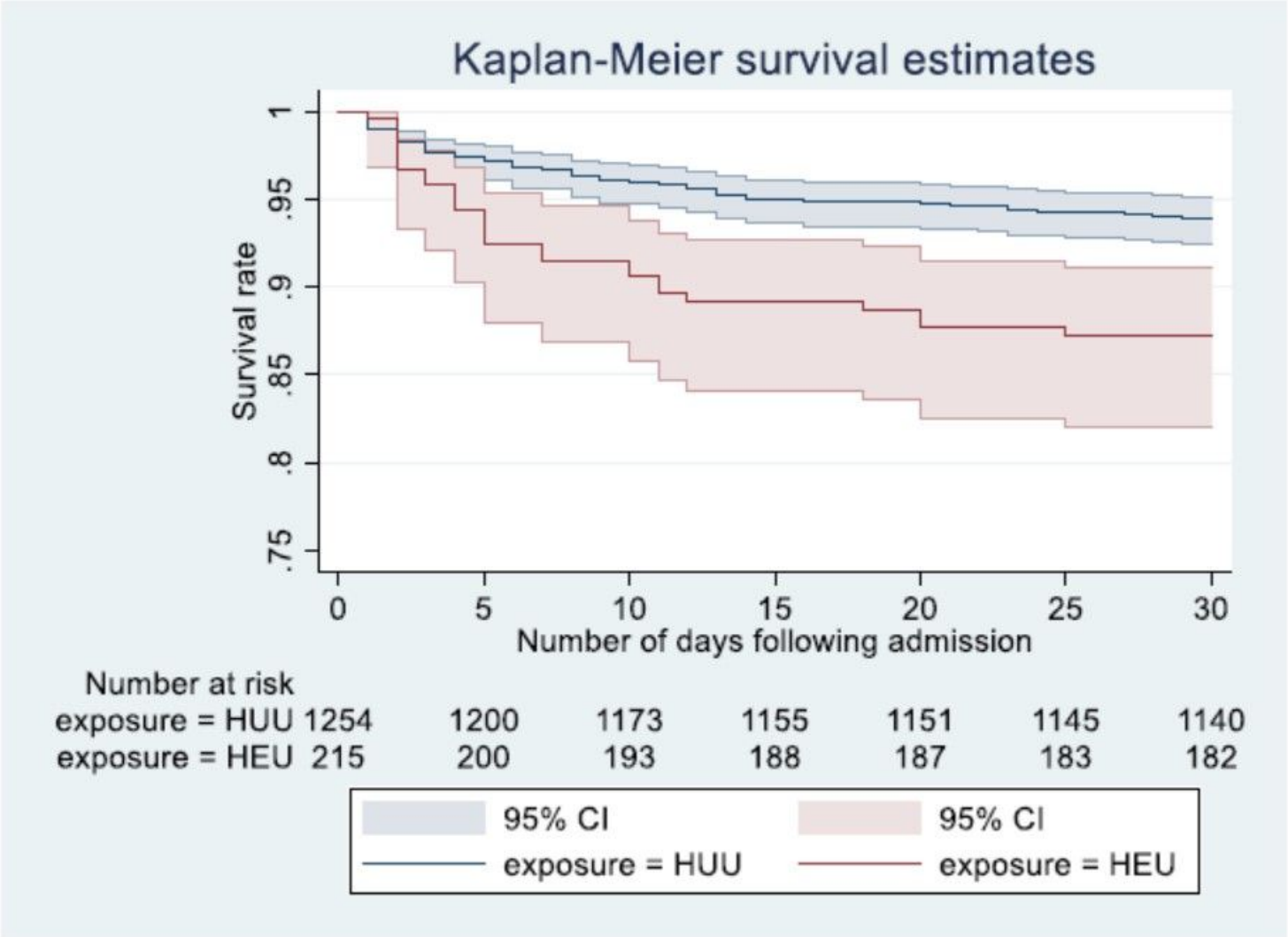

Figure 2

Kaplan-Meier survival curve showing survival rate versus number of days following hospital admission

Abbreviations: HUU-HIV unexposed uninfected, HEU- HIV exposed uninfected; Logrank test for equality of survivor functions, p = 0.0004

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementHospitalcourseinHEUvsHUUCHAINchildren11Apr24final.docx