Differences in Morbidity Between Breastfed HIV-Exposed Uninfected and HIV-Unexposed Infants in the Era of Universal Maternal Antiretroviral Therapy

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Abstract

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Background: HIV-exposed uninfected children (CHEU) experience higher morbidity and mortality than HIV-unexposed children (CHU), despite global scale-up of antiretroviral therapy (ART) in pregnancy. Evaluating the risk of morbidity in breastfed CHEU and CHU in the era of highly effective maternal ART and identifying socio-demographic characteristics associated with increased morbidity will inform future interventions to improve health in CHEU.

Methods: Study participants included 172 CHEU and 164 CHU, born to enrolled pregnant women living with and without HIV, and followed through 12-months of age. Data on infant illness, along with information on additional biological and social factors, was collected via maternal report at all study visits. Differences in time to first episode of any illness and time of first episode of acute diarrhea (defined as ≥3 loose or watery stools per day) were assessed overall as well as stratified by HIV-exposure using adjusted hazard ratio (aHR) estimates (and corresponding 95% confidence intervals [CIs]) from multivariate Cox proportional hazards regression models. The final models for both primary outcomes included household food insecurity, maternal educational attainment, and breastfeeding duration, with the addition of maternal depression in the model for any illness, and marital status in the model for acute diarrhea.

Results: Between birth and 12 months, children experienced 299 episodes of any illness (156 CHEU; 146 CHU) and 55 episodes of acute diarrhea (22 CHEU; 33 CHU). Overall, mothers reported optimal breastfeeding practices, with 86.9% still breastfeeding at their 12-month visit (83.7% CHEU; 90.2% CHU). In the adjusted model, HIV-exposure was not associated with first episode of any illness (aHR=1.06, 95% CI 0.83 – 1.36, p=0.640). However, it was associated with a decreased risk of acute diarrhea (aHR=0.36; 95% CI 0.30, 0.96; p=0.036). Moderate food insecurity (aHR=2.27, 95% CI 1.10, 4.67, p=0.026) and being previously married (aHR=2.24, 95% CI 1.16, 4.32, p=0.016) were associated with increased risk of acute diarrhea. Moderate-severe maternal depression was associated with an increased risk of any illness (aHR=1.94, 95% CI 1.00, 3.79, p=0.052).

Conclusions: In contrast to earlier studies, CHEU experienced no difference in risk of illness and a decreased risk of acute diarrhea compared to CHU in the first 12-months of life. Future studies are needed to evaluate the effects of HIV prevention interventions and social support strategies on infant morbidity.

Introduction

Global scale up and expansion of access to antiretroviral therapy (ART) among pregnant and breastfeeding women has reduced the risk of perinatal HIV transmission from 25-30% in 1994[1] to 2-5% by 2005[2], resulting in a growing population of HIV-exposed but uninfected children (CHEU). It is estimated that there are more than 15 million CHEU globally, with an additional one million born each year[3]. The majority (90%) of these children live in sub-Saharan Africa, with just five countries in sub-Saharan Africa accounting for half of the global population of CHEU[4].

Despite being HIV-negative, CHEU have been shown to experience higher morbidity and mortality than HIV-unexposed children (CHU), even in the current global context of widespread access to ART. Pooled data from studies conducted in sub-Saharan Africa between 2004-2015, showed a cumulative mortality risk of 11% in CHEU at 24 months of age, two-fold the mortality risk compared to CHU[5]. CHEU are more likely to be preterm, have a lower birthweight, and be small-for-gestational age than CHU – all of which are significant risk factors for higher morbidity, (including hospitalization) and mortality[6]. Numerous studies over the past decades have found that CHEU experience an increased risk of infectious morbidity compared to CHU, including increased incidence of diarrhea, respiratory infections, and infectious cause hospitalizations[6–8]. Limited data from more recent studies suggest that growth and morbidity differences remain between CHEU and CHU throughout childhood, with other studies finding school-aged CHEU have poorer long-term neurocognitive outcomes than CHU[9–12]. While women living with HIV (WLWH) today are more likely to be virologically suppressed during pregnancy and postpartum given more efficacious ART regimens, the consequences of *in utero* exposure to HIV and ART on outcomes in CHEU remain poorly understood[13].

Several biological mechanisms have been proposed to explain the morbidity differences observed in CHEU and CHU. *In utero* HIV-exposure has similarities to many chronic infections in pregnancy, in that maternal immune activation can lead to placental inflammation which induces

the fetal innate immune system, causing heightened inflammation and modifying responses to early infection[13,14]. ART toxicity has also been associated with altered innate and adaptive immune responses in CHEU, which may increase susceptibility to infection[14]. In addition to immune dysfunction, metabolic alterations due to dysregulation of the mitochondria from prenatal HIV and ART-exposure, have been observed in CHEU that have lasting implications in immune response, growth, and development[15,16]. Along with exposure to HIV and ART, other risk factors related to social determinants (e.g., household food insecurity, lower levels of maternal education) or life style (e.g., suboptimal breastfeeding practices) have been associated with poor health outcomes in CHEU[8,17,18].

We hypothesized that CHEU would experience higher rates of morbidity in the first 12-months of life than CHU, despite universal maternal ART with breastfeeding. In addition, we hypothesized that adverse social and economic factors such as poverty, household food insecurity, and maternal unemployment would be associated with increased risk of any illness and acute diarrhea both overall and among CHEU and CHU. Study findings will assist in identifying key factors associated with increased morbidity risk and provide much needed data to inform future interventions to reduce morbidity and mortality in CHEU across sub-Saharan Africa.

METHODS

Study design and setting

This analysis used data from the Tunza Mwana study, an on-going prospective cohort study of mother-infant dyads in Kenya. The overarching objective of the Tunza Mwana study is to determine how maternal HIV infection impact human breast milk oligosaccharides (HMOs), and the influence of HMOs on the infant gut microbiome and subsequent health outcomes of CHEU and CHU from birth to 3-years of age. Pregnant women living with and without HIV were enrolled at two hospital-based antenatal clinics (Migori County Referral Hospital and St. Joseph's Mission Hospital) in Migori, Kenya between November 2021 and November 2022. Study participants and their infants were followed until 12 months postpartum.

Study participants

Pregnant women attending antenatal care at either facility were approached by study staff and informed of the study procedures. If interested in participating, women provided oral consent and answered questions about their pregnancy and HIV-status to confirm eligibility. To be eligible, pregnant women had to be aged 18-40 years, between 28–42 weeks' gestation, have planned to primarily breastfeed their infant for at least 6 months and intended to remain within the study catchment area for at least 24 months. All WLWH were on ART and had to agree to continue to use prevention-of-mother-to-child-transmission (PMTCT) services following the birth of their child. Pregnant women outside of the specified age range or gestational window were excluded, as well as those who did not plan on primarily breastfeeding, intended on delivering outside the catchment area, or were not willing to disclose HIV-status at screening. In addition, pregnant women who had been diagnosed with hypertension, pre-eclampsia, or other serious medical condition that increased their likelihood of needing an early induction of labor or scheduled Caesarean section were excluded.

Overall, 350 pregnant women (175 WLWH and 175 HIV-uninfected) were enrolled (**Figure 1**), with 6 mothers choosing to withdraw from the study prior to their delivery visit. In addition, two mother-child dyads were terminated by study investigators for no longer meeting the inclusion criteria (one child had a congenital anomaly and one dyad relocated to Tanzania) and two were lost during study follow-up. Six infants died prior to their 12-month visit, of which four were neonatal deaths. In total, 336 (96%) mother-infant dyads remained on-study following delivery and 328 dyads remained enrolled at the 12-month follow-up visit (166 WLWH/CHEU, 162 HIV-negative/CHU). This study was approved by the University of Washington Institutional Review Board, the Kenya Medical Research Institute Scientific and Ethics Review Unit, and the Kenya National Commission for Science, Technology and Innovation. All participants provided written informed consent in their preferred language (Kiswahili, Luo, Kuria, or English).

Data Collection

At enrollment, participants were interviewed using a standardized questionnaire by trained study staff to obtain demographic and socio-economic information and medical and obstetric history, including medications and antibiotics. HIV-status was confirmed among WLWH and data on ART regimen and duration, cotrimoxazole (CTX) prophylaxis, and HIV viral load was collected. Maternal anthropometry (weight, height, and mid-upper arm circumference) was collected from all pregnant women. Medical records were additionally used to abstract relevant health information.

Following enrollment, participants returned to the study clinic with their infant within 7 days of delivery, at weeks 3 and 6, and at months 3, 6, 9, and 12. Standardized questionnaires were administered by trained staff at all visits to ascertain information on the health of the mother-child dyad and acquire information on any social changes (e.g. marital or relationship status, household income, living conditions). Mothers were asked if their child had any recent history of illness, clinic visits, or hospitalization since their last study visit. Additional questions on symptoms were asked

if there was indication of child illness, and clinic or hospital medical records were obtained as needed. Information on maternal illness, maternal mental health, maternal diet, infant feeding, and household food insecurity were collected at each study visit. Maternal and infant anthropometric measurements were taken at all visits.

Among CHEU, data on antiretroviral (ARV) prophylaxis was collected at all study visits and CTX prophylaxis was collected starting at the 6-week visit. All CHEU had HIV testing in accordance with Kenyan guidelines. Child HIV PCR testing was conducted at age 6-weeks, 6-months, and 12-months, and HIV antibody testing was conducted at 18 months of age.

Primary Outcomes

Primary outcomes of interest were first incidence of infant illness and first incidence of acute diarrhea. Incidence of illness and acute diarrhea were ascertained based on maternal report at study visits, or from records of a clinic or hospital visit for illness. Reportable symptoms included fever, cough, difficulty breathing, lethargy, diarrhea, vomiting, lack of eating or drinking, weight loss, restlessness, rash/itching, ear problems, oral thrush, pneumonia, jaundice, and malaria. Acute diarrhea was defined as ≥3 loose stools in a 24-hour period, with or without blood in the stool.

Covariates

Covariates of interest included those identified *a priori* based on known associated risk factors for morbidity and sociodemographic and biological factors that may be relevant. Infant characteristics included infant sex (male/female), preterm birth (defined as <37 weeks' vs. ≥37 weeks' gestation), and low birthweight (≤2500 g vs. ≥2500 g). Maternal characteristics included educational attainment (primary or below vs. secondary and above), marital status (married/unmarried), employment status (employed vs. unemployed/homemaker), depression at enrollment (none, minimal to mild, moderate to severe), socioeconomic status (quintile wealth

index), household food insecurity (secure, mild, moderate, severe), and breastfeeding duration (number of days from delivery*)*. For analyses among CHEU, additional factors considered included: maternal ART regimen (dolutegravir [DTG]-based ART vs. other ART), timing of ART initiation (prior to vs. during pregnancy), and maternal HIV viral suppression prior to delivery (<1000 copies/mL).

Prior studies on perinatal HIV-exposure identified several covariates associated with increased infectious morbidity among CHEU. Given the breadth of evidence supporting these associations, the following variables were identified *a priori* and included in all adjusted models: breastfeeding duration, maternal education, and household food insecurity[7,19–23].

Data Analysis

Descriptive statistics were used to summarize sociodemographic and clinical characteristics of the overall study population and stratified by infant HIV-exposure status. Incidence of each primary outcome, person-time, and incidence rate per 100 child-months was calculated for each primary outcome for the overall cohort and by HIV-exposure status. Kaplan-Meier survival curves of cumulative incidence were constructed for any illness and acute diarrhea (**Figure 2**), both for the total study population and by HIV-exposure status. Associations of HIV-exposure status with time to first episode of any illness and time to first episode of acute diarrhea, in separate models, were examined using Cox Proportional-Hazard models. Subjects were censored from the analysis at the last known HIV-negative test date for children who seroconverted, at the last data of contact if lost-to-follow-up, or at the end of the 12-month study period. Each covariate was individually evaluated for associations with each primary outcome (any illness and acute diarrhea) using univariate analysis. Those that were associated with each primary outcome (at $P \leq 0.05$) were included in the respective multivariate models, along with those identified *a priori.* Correlation between covariates was tested before inclusion in each respective multivariate model by using variance inflation factors (VIF) to detect multicollinearity.

The final models for both primary outcomes included household food insecurity, maternal educational attainment, and breastfeeding duration, with the addition of maternal depression in the model for any illness, and marital status in the model for acute diarrhea. In secondary analysis, we further evaluated whether each covariate was univariately associated with each primary outcome, stratified by HIV-exposure status. Low power limited the ability to assess associations with covariates in the stratified analysis, and adjusted models were unstable due to the lack of convergence for several covariates. All analyses were performed using R version 4.3.3 (R Core Team, 2024).

RESULTS

Among participants, 47.3% of infants were female, with a median gestational age of 39 weeks (IQR: 38-40 weeks) (**Table 1**). A large majority of infants were breastfeeding at their 6-month visit (96.1%) and at their 12-month visit (86.9%). Compared to women living without HIV, more WLWH were in the lowest two wealth quintiles (48.2% vs 32.1%), reported moderate to severe food insecurity in the past month (66% vs 50.9%), and had lower levels of educational attainment (56.4% vs 32.1% with primary level or below). Amongst WLWH, 76.7% had started ART prior to conception, with 85.5% virally suppressed at enrollment, and 87.8% on the WHO recommended first-line integrase inhibitor DTG-based ART regimen.

In the first 12-months, overall incidence of any illness was 20.23 per 100 infant-months (299 total episodes) and overall incidence of acute diarrhea was 1.48 per 100 infant-months (55 total episodes) (**Table 2, Figure 2**). A higher incidence of any illness was observed among CHEU (153 episodes; 256.95 per 100 child-years) compared to CHU (146 episodes; 229.47 per 100 child-years; p=0.31), while CHU had a higher incidence of acute diarrhea (33 episodes; 22.01 per 100 child-years) compared to CHEU (22 episodes; 13.81 per 100 person-years), although these differences were not statistically significant (p=0.31 and 0.11, respectively).

In multivariate analysis adjusting for infant HIV exposure, household food insecurity, maternal education and breastfeeding duration, moderate to severe depressive symptoms at enrollment were associated with higher risk of any infant illness compared to no depressive symptoms (aHR=1.94, 95% CI 1.00, 3.79; p=0.052) (**Table 3**). No other factors were found to be associated with any infant illness in the overall cohort.

In univariate analysis, moderate household food insecurity in pregnancy vs. food secure (HR=2.09, 95% CI 1.04, 4.20, p=0.039) and being previously married vs. married (HR=2.0, 95% CI 1.05, 3.80, p=0.034) were associated with an increased risk of acute diarrhea in the first 12 months (**Table 4**). These associations remained statistically significant after adjusting for infant HIV exposure status, breastfeeding duration, and maternal education (**Table 4**). In addition, in

adjusted analysis, CHEU had a decreased risk of acute diarrhea compared to CHU (aHR=0.54, 95% CI 0.30, 0.96; p=0.036).

To further evaluate factors associated with risk of any illness and acute diarrhea among CHEU and CHU, we conducted a secondary univariate analysis stratified by infant HIV exposure status. Among CHEU, only preterm vs. term birth was associated with risk of illness (**Appendix Table 1**). Among CHU, moderate household food insecurity vs. secure (p=0.044), 2-4 prior pregnancies vs. first-time mothers (p=0.037), and moderate-severe vs. no depressive symptoms (p=0.036) were associated with increased risk of illness while secondary or higher education vs. primary or below was associated with decreased risk of illness (p=0.009). In stratified analysis for acute diarrhea, CHEU in households reporting moderate food insecurity vs. being secure had increased diarrhea risk (p=0.046) (**Appendix Table 2**). For CHU, marital status was the only covariate associated with acute diarrhea, with infants born to mothers who were previously married vs. currently married or cohabiting having an increased risk (p=0.025).

DISCUSSION

In this prospective longitudinal cohort study of 336 mother-infant dyads in Kenya, we observed higher incidence rate of any illness and lower incidence rate of acute diarrhea among CHEU, compared with CHU. Infant HIV-exposure was not significantly associated with risk of illness in the first 12-months but was found to significantly decrease the risk of acute diarrhea. Additional sociodemographic factors were also identified, with maternal depression associated with risk of any illness and household food insecurity and marital status associated with risk of acute diarrhea.

We observed a low incidence of acute diarrhea during the study period, with a cumulative incidence rate of 1.48 per 100 child-months, and CHEU were found to have a decreased risk of acute diarrhea compared to their CHU counterparts. This is in contrast to earlier studies conducted prior to universal maternal ART and with suboptimal breastfeeding practices, which found that on average CHEU had a 36% increased risk of acute diarrhea and a 9% increased risk of chronic diarrhea compared to CHU[8,22,24,25]. The decreased risk observed amongst our participants may be in part due to the high rates of breastfeeding reported across the cohort, with 87% of all mothers reporting breastfeeding at the 12-month study visit. Breastfeeding has been shown to be a critical method of reducing diarrhea in infants, with early initiation and exclusive breastfeeding associated with reductions in incidence and duration of diarrhea in infants[26]. In studies among CHEU, exclusive breastfeeding has been found to decrease incidence of infectious illness, including diarrhea, in the first 12-months of life[21,27]. Our high breastfeeding duration therefore could have contributed to the low overall incidence of acute diarrhea events observed across all infants in the 12-month follow-up period. Though we did not find any significant association with breastfeeding in our analysis, this could be due to the low variance in breastfeeding duration across the cohort.

Though previously observed to have higher incidence of diarrhea, recent studies in the context of lifelong maternal ART and prophylactic cotrimoxazole (CTX) for children born to WLWH have also found that CHEU may no longer have an increased risk of diarrhea during infancy compared to CHU[22,28,29]. A study conducted in Kisumu County, Kenya, from 2011-2016, enrolled a similar patient cohort to our study, with all WLWH receiving tenofovir (TDF)-based ART and reporting high rates of breastfeeding, along with HIV-exposed infants receiving CTX prophylaxis per the Kenyan Ministry of Health guidelines[29]. Analysis at 24-months found that CHEU and CHU had similar growth characteristics and immune profiles, with CHEU having a decreased risk of malaria and respiratory illness, and no difference in risk of diarrhea compared to CHU[29]. Another prospective cohort study conducted from 2012 – 2013 in South Africa also enrolled WLWH on TDF-based ART with infants receiving CTX prophylaxis starting at 6-weeks through cessation of breastfeeding[22]. Analysis at 6-months found no difference in diarrhea-associated clinic visits between CHEU and CHU, though CHEU were found to be at greater risk of hospitalization for diarrhea[22]. Both studies were conducted prior to the current WHO recommended first-line DTG-based ART, which has been shown to be more effective than previous regimens[30]. Reductions in diarrhea incidence may be secondary to CTX prophylaxis in CHEU, which has been supported in other studies, but the overall clinical benefits of CTX alone in preventing diarrhea are unclear[31,32].

Household food insecurity and marital status were both associated with an increased risk of acute diarrhea in the final model. Infants in households with moderate food insecurity (vs. secure) and those born to mothers who were previously married (vs. currently married or cohabiting) had a two-fold increase in risk of acute diarrhea. In our cohort, WLWH were more likely to experience moderate-severe food insecurity and be previously married compared to mothers living without HIV. These findings align with other studies, which have found food insecurity associated with an increased risk of infectious illness (including diarrhea) and that WLWH were more likely to experience household food insecurity than those living without HIV[17,33]. The impact of marital status on infant health is less researched, however numerous studies have

shown that infants born to unmarried women have a higher incidence of adverse birth outcomes, including low birthweight and preterm birth[34]. In our study, marital status could be a marker of socioeconomic status, such as a reduction in overall household income. Future studies are needed to further examine the relationship between marital status and infectious morbidity, particularly in low- and middle-income countries.

Maternal depression was the only factor found to be associated with a risk of any illness in the first 12-months of life. There is limited research on how depression during pregnancy effects infant morbidity post-delivery, however postpartum depression has been associated with increased risk of adverse infant outcomes, including stunting, malnutrition, and infectious illnesses[35–38]. Whereas other studies have found that WLWH are more likely to have depression than women without HIV, our study noted similar rates of maternal depression at enrollment[39]. In stratified analyses, we were surprised to find that maternal depression was found to only be significantly associated with illness in CHU, which could be due to the protective role of resilience in WLWH. Resilience is the positive psychological adaptation to adversities, and a prior study found that resilience acted as a moderator for co-existing adversities in mothers (including HIV) and depressive symptoms[40]. However, the effects of maternal depression on infant health outcomes remains poorly understood, with even fewer studies conducted in low- and middle-income countries.

While our study had many strengths, including longitudinal follow-up with high retention at 12-months, there are several limitations. There was early attrition in the loss to follow-up of nine pregnant women between enrollment and delivery, the majority of whom were women without HIV (3%; 6/175) which may have introduced selection bias. Standardized questionnaires were administered at all visits by trained study staff to reduce interviewer bias, however information on child health, such as instances of cough, diarrhea, and fever, were reported by mothers and therefore subject to recall bias. Though additional information on hospitalizations or clinic visits for illness was obtained via medical records, reliance on self-reporting of infant symptoms may

have limited the total ascertainment of episodes, particularly in cases that were less severe. Our ability to identify associations between HIV-exposure status and other covariates will be attenuated by misclassification of the outcome; therefore, the associations we report may be an underestimate. Additionally, by examining episode of illness as a singular category we are lacking specificity on the potentially different mechanisms that may be driving differences in morbidity between CHEU and CHU.

There were very few episodes of acute diarrhea reported in infants in the first 12-months, and therefore our analyses for this outcome may have limited statistical power. This may be in part due to most infants still being breastfed at 12-months, as diarrhea is less likely to occur while infants are still exclusively breastfed. Our study also used a more conservative definition of diarrhea than some previous studies by defining an episode of diarrhea to be ≥3 episodes of loose stool within 24-hours, as opposed to other studies whose definition included any incidence of loose stool as an episode of diarrhea. Future analyses should involve follow up for a longer study period (first 24-months) or include larger sample size to improve study power.

The study structure, and particularly the lactational support provided to all mothers, likely contributed to extremely high rates of reported breastfeeding. While previous recommendations by the WHO discouraged breastfeeding amongst WLWH, in 2010 the WHO released updated guidelines recommending that WLWH on ART exclusively breastfeed for the first 6 months of life, and continue to breastfeed for 24 months or longer[41]. Despite this, many WLWH continue to fear that breastfeeding may lead to vertical HIV transmission, with recent studies of CHEU and CHU in South Africa finding that at 6 months of age, only 47% of CHEU were breastfed, with breastfeeding rates continuing to decline over time[42]. As of 2020, only 60% of Kenyan mothers reported exclusively breastfeeding their infant from 0-5 months, while mixed-feeding remains a deeply engrained cultural practice[43]. All mothers had planned on exclusively breastfeeding their infant as part of the study inclusion criteria, and while on study received personalized lactational support at all study visits which may have led to longer breastfeeding duration. It is also possible

that participants reported higher rates of breastfeeding than what was practiced. Regardless, we observed significantly longer breastfeeding durations amongst mothers in this study than typically seen in WLWH and women without HIV, which would reduce generalizability to women and infants with shorter breastfeeding duration. Another recent study found that CHEU and CHU had similar rates of breastfeeding at 6-weeks (96.1% vs. 99.9%) but significantly fewer CHEU were still breastfed at 9-months (72.4% vs. 98.2%)[44]. A secondary analysis of this data, currently under review, additionally found that while WLWH had a 25% higher prevalence of exclusive breastfeeding during the first 6-months, the prevalence of continued breastfeeding was 27% lower in WLWH at 9-month compared to their HIV-uninfected counterparts. Data on exclusive breastfeeding within our cohort was unavailable at the time of analysis but will be examined in future analyses to further assess associations with infant morbidity.

All women in this study were enrolled after attending antenatal care while pregnant and continued to have regular contact with medical professionals as they returned to clinic for study visits. Therefore, our findings are not generalizable to women and infants with poor access to health care. Information was collected at all study visits on covariates of interest, including infant ARV regimen and timing, initiation of CTX prophylaxis, exclusive breastfeeding. However, data on several covariates of interest were not available for inclusion at the time of analysis. Therefore, future analyses should examine the effects of fixed and time-varying covariates of interest on recurrent events of illness, including respiratory infection and diarrhea, to further evaluate whether differences in morbidity between CHEU and CHU persist.

In this study of CHU and CHEU under conditions of universal maternal ART and optimal breastfeeding practices, CHEU experienced a similar risk of illness and a decreased risk of acute diarrhea in the first 12-months of life compared to CHU. HIV-exposure was not associated with risk of illness but was found to decrease the risk of diarrhea. Several sociodemographic factors were found to be associated with infant morbidity, including maternal depression being associated with an increased illness, while household food insecurity and marital status were associated with

an increased risk of diarrhea. While results of this study contrast previous assumptions of *in-utero* HIV-exposure and risk of infant morbidity, they support growing evidence that CHEU may no longer be at a significantly greater risk of morbidity compared to CHU in the context of lifelong maternal ART, infant CTX prophylaxis, and optimal breastfeeding. Future studies are needed to evaluate the effects of targeted maternal and child HIV interventions and social support strategies on infant morbidity.

TABLES AND FIGURES:

Figure 1 Flow diagram of study participants

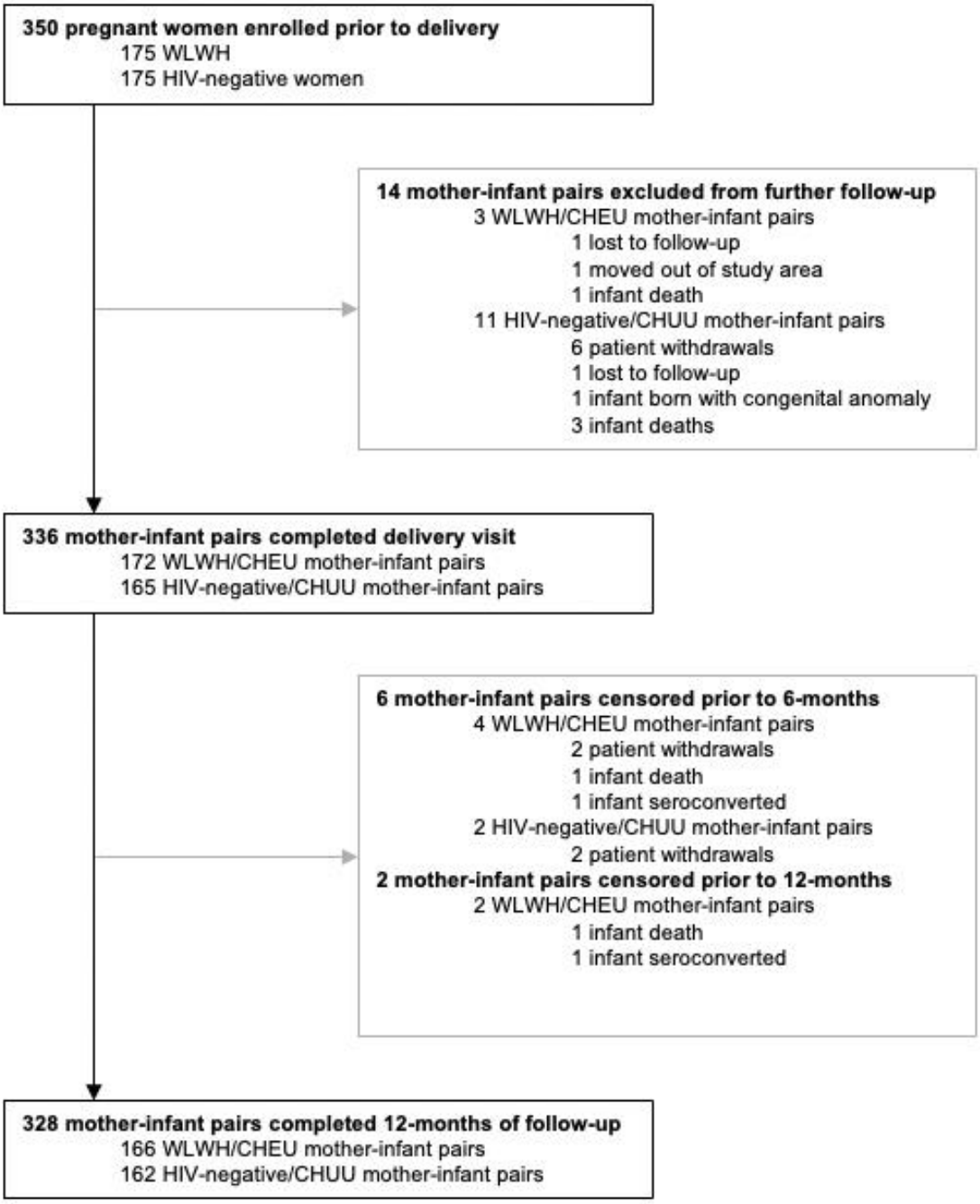


Table 1 Baseline maternal and infant characteristics by infant HIV-exposure status

	% (n) or median (IQR)		
	Overall cohort *N = 336*	**HIV-exposed uninfected infant** n = 172	**HIV-unexposed infant** n = 164
Household characteristics:			
Crowding (≥3 per room)	20.2 (68)	20.3 (35)	20.0 (33)
Household wealth (quintile)			
Wealthiest	7.7 (26)	5.2 (9)	10.3 (17)
Wealthy	23.4 (79)	16.9 (29)	30.3 (50)
Middle	28.5 (96)	29.7 (51)	27.3 (45)
Poor	24.9 (84)	30.2 (52)	19.4 (32)
Poorest	15.4 (52)	18.0 (31)	12.7 (21)
Food insecurity			
Secure or mild insecurity	41.3 (138)	33.7 (57)	49.1 (81)
Moderate to severe insecurity	58.7 (196)	66.3 (112)	50.9 (84)
Maternal characteristics:			
Age (years)	26.9 (22.9 – 32.6)	29.0 (25.5 – 33.8)	24.6 (21.8 – 28.9)
Mid-upper arm circumference (cm)	27.0 (25.2 – 29.5)	27.0 (25.0 – 29.4)	27.1 (25.4 – 29.5)
Marital status			
Married or cohabiting	86.4 (291)	85.5 (147)	87.3 (144)
Previously married	13.6 (46)	14.5 (25)	12.7 (21)
Unemployed	49.0 (165)	41.9 (72)	56.4 (93)
Educational attainment			
Primary or below	44.5 (150)	56.4 (97)	32.1 (53)
Secondary or higher	55.5 (187)	43.6 (75)	67.9 (112)
Parity			
Primiparous	19.9 (67)	7.0 (12)	33.3 (55)
2-4	58.8 (198)	63.4 (109)	53.9 (89)
>4	20.8 (70)	28.5 (49)	12.7 (21)
Maternal depression at enrollment			
None	33.2 (112)	34.3 (59)	32.1 (53)
Minimal to mild	63.5 (214)	62.2 (107)	64.8 (107)
Moderate to severe	3.3 (11)	3.5 (6)	3.0 (5)
Antiretroviral therapy (ART) started preconception	-	76.7 (132)	-
Dolutegravir (DTG)-based ART regimen	-	87.8 (151)	-
Viral suppression at enrollment			
Lower than detectable limit (<1000 copies/mL)	-	85.5 (147)	-
Missing	-	8.1 (14)	-
Infant characteristics:			
Female sex	47.3 (159)	47.8 (82)	47.0 (77)
Preterm delivery (<37 weeks' gestation)	9.5 (32)	10.5 (18)	8.5 (14)
Gestational age at delivery (weeks)	39 (38 – 40)	39 (38 – 40)	39 (38 – 40)
Low birthweight (≤2500 grams)	6.5 (22)	6.4 (11)	6.7 (11)
Breastfeeding characteristics:			
Reported breastfeeding at 6 mo. visit	96.1 (323)	95.3 (164)	97.0 (159)
Reported breastfeeding at 12 mo. visit	86.9 (292)	83.7 (144)	90.2 (148)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range
Missing values that exceeded 5% are included.

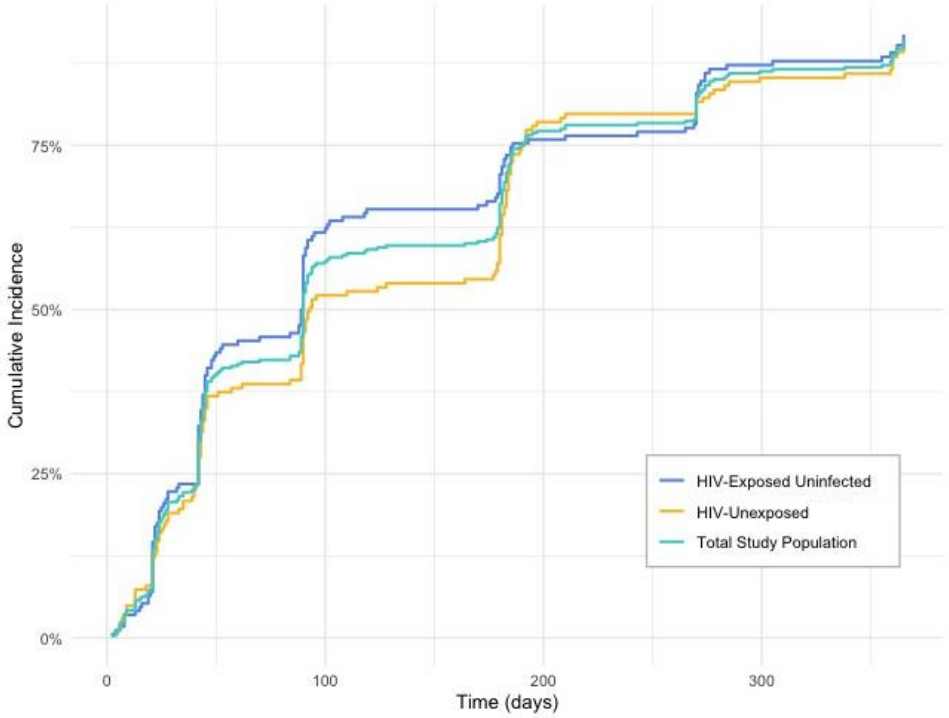
Table 2 Incidence of first episode of any illness and acute diarrhea in the first year of life in the total study population and by infant HIV-exposure status

	Overall cohort N=336	**HIV-unexposed** n=164	**HIV-exposed uninfected** n=172
First episode of any illness			
Events	299	146	153
Person-time, child-years	123.17	63.62	59.55
Incidence rate, 100 child-months	20.23	19.12	21.41
Unadjusted HR (95% CI)		Ref.	1.13 (0.89 – 1.41)
First episode of acute diarrhea			
Events	55	33	22
Person-time, child-years	309.18	149.92	159.27
Incidence rate, 100 child-months	1.48	1.83	1.15
Unadjusted HR (95% CI)		Ref.	0.64 (0.37 – 1.10)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; Ref, Reference Category

Figure 2 Cumulative incidence of any illness (A) and acute diarrhea (B) in the first year of life among the total study population and by infant HIV-exposure status

(A) First episode of any illness



(B) First episode of acute diarrhea

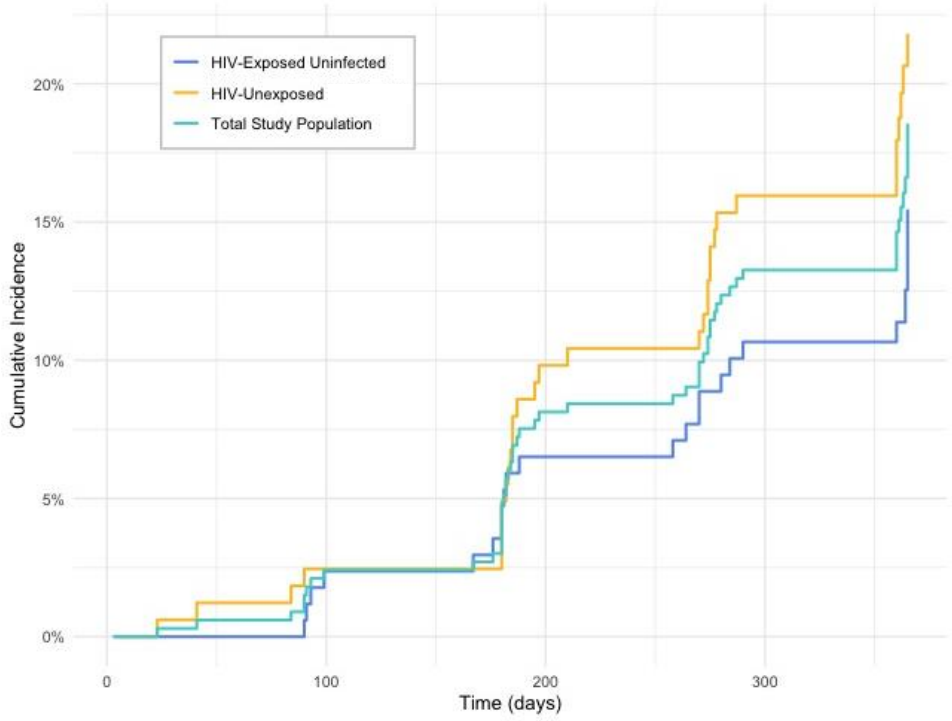


Table 3 Covariates and risk of first episode of any illness in the first year of life among the total study population

	Unadjusted HR (95% CI)	*p-value*	*Adjusted HR (95% CI)**	*p-value*
HIV-exposed uninfected infant	1.12 (0.90 – 1.41)	0.310	1.06 (0.83 – 1.36)	0.640
Household characteristics:				
Crowding (≥3 per room)	1.23 (0.93 – 1.62)	0.153		
Household wealth (quintile)				
Wealthiest	Ref.			
Wealthy	0.96 (0.60 – 1.56)	0.882		
Middle	1.20 (0.75 – 1.92)	0.442		
Poor	1.29 (0.80 – 2.07)	0.296		
Poorest	1.29 (0.78 – 2.14)	0.321		
Food insecurity				
Secure	Ref.		Ref.	
Mild insecurity	1.08 (0.77 – 1.51)	0.670	0.99 (0.69 – 1.43)	0.720
Moderate insecurity	1.15 (0.83 – 1.60)	0.396	1.08 (0.77 – 1.53)	0.697
Severe insecurity	1.03 (0.77 – 1.38)	0.847	0.99 (0.74 – 1.53)	0.785
Maternal characteristics at enrollment:				
Marital status				
Married or cohabiting	Ref.			
Previously married	0.79 (0.56 – 1.11)	0.169		
Unemployed	1.24 (0.99 – 1.65)	0.063		
Educational attainment				
Primary or below	Ref.		Ref.	
Secondary or higher	0.85 (0.68 – 1.07)	0.175	0.87 (0.67 – 1.13)	0.282
Parity				
Primiparous	Ref.			
2-4	1.32 (0.98 – 1.78)	0.071		
>4	1.40 (0.97 – 2.01)	0.070		
Maternal depression				
None	Ref.		Ref.	
Minimal to mild	1.15 (0.90 – 1.48)	0.250	1.18 (0.92 – 1.52)	0.170
Moderate to severe	1.89 (0.98 – 3.63)	**0.056**	1.94 (1.00 – 3.79)	**0.052**
ART started preconception	0.92 (0.61 – 1.37)	0.667		
DTG-based ART regimen	0.96 (0.58 – 1.60)	0.989		
Viral suppression (<1000 copies/mL)	0.70 (0.35 – 1.37)	0.296		
Infant characteristics:				
Female sex	0.88 (0.70 – 1.10)	0.252		
Preterm delivery (<37 weeks' gestation)	0.72 (0.50 – 1.05)	0.090		
Low birthweight (≤2500 grams)	0.75 (0.47 – 1.19)	0.218		
Breastfeeding duration (days)	1.00 (1.00 – 1.00)	0.643	1.00 (1.00 – 1.00)	0.614

**Adjusted for HIV-exposure, food insecurity, maternal educational attainment, maternal depression, and breastfeeding duration*
HR, Hazard Ratio; CI, Confidence Interval; Ref, Reference Category

Table 4 Covariates and risk of first episode of acute diarrhea in the first year of life among the total study population

	Unadjusted HR (95% CI)	*p-value*	*Adjusted HR (95% CI)**	*p-value*
HIV-exposed uninfected infant	0.64 (0.37 – 1.10)	0.110	0.54 (0.30 – 0.96)	**0.036**
Household characteristics:				
Crowding (≥3 per room)	1.23 (0.93 – 1.62)	0.153		
Household wealth (quintile)				
Wealthiest	Ref.			
Wealthy	1.6 (0.46 – 5.55)	0.463		
Middle	2.21 (0.66 – 7.40)	0.197		
Poor	1.32 (0.37 – 4.69)	0.665		
Poorest	0.70 (0.16 – 3.12)	0.637		
Food insecurity				
Secure	Ref.		Ref.	
Mild insecurity	1.08 (0.47 – 2.50)	0.852	1.29 (0.54 – 3.12)	0.565
Moderate insecurity	2.09 (1.04– 4.20)	**0.039**	2.27 (1.10 – 4.67)	**0.026**
Severe insecurity	0.89 (0.42 – 1.89)	0.764	0.94 (0.44 – 2.03)	0.883
Maternal characteristics at enrollment:				
Marital status				
Married or cohabiting	Ref.		Ref.	
Previously married	2.0 (1.05 – 3.80)	**0.034**	2.24 (1.16 – 4.32)	**0.016**
Unemployed	0.93 (0.55 – 1.58)	0.796		
Educational attainment				
Primary or below	Ref.		Ref.	
Secondary or higher	1.03 (0.61 – 1.76)	0.901	0.87 (0.49 – 1.55)	0.645
Parity				
Primiparous	Ref.			
2-4	0.77 (0.40 – 1.47)	0.424		
>4	0.88 (0.40 – 1.93)	0.752		
Maternal depression				
None	Ref.			
Minimal to mild	0.89 (0.51 – 1.56)	0.690		
Moderate to severe	1.12 (0.26 – 4.79)	0.882		
ART started preconception	5.39 (0.72 – 40.20)	0.100		
Dolutegravir (DTG)-based ART regimen	2.74 (0.37 – 20.40)	0.324		
Viral suppression (<1000 copies/mL)	0.68 (0.16 – 2.91)	0.601		
Infant characteristics:				
Female sex	0.80 (0.47 – 1.36)	0.408		
Preterm delivery (<37 weeks' gestation)	0.63 (0.23 – 1.73)	0.368		
Breastfeeding duration (days)	1.00 (0.99 – 1.00)	0.158	1.00 (0.99 – 1.00)	0.086

**Adjusted for infant HIV exposure, food insecurity, marital status, maternal educational attainment, and breastfeeding duration*
Low birthweight could not be included due to small numbers
HR, Hazard Ratio; CI, Confidence Interval; Ref, Reference Category

APPENDIX

Appendix Table 1 Covariates and risk of time to first episode of any illness in the first year of life by infant HIV-exposure status

	HIV-Exposed Uninfected		HIV-Unexposed	
	HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*
Household characteristics:				
Crowding (≥3 per room)	1.18 (0.80 – 1.74)	0.405	1.31 (0.88 – 1.95)	0.186
Household wealth (quintile)				
Wealthiest	Ref.		Ref.	
Wealthy	1.02 (0.46 – 2.26)	0.967	0.93 (0.51 – 1.70)	0.809
Middle	1.18 (0.55 – 2.50)	0.673	1.21 (0.66 – 2.22)	0.537
Poor	1.4 (0.66 – 2.97)	0.375	1.14 (0.60 – 2.16)	0.687
Poorest	1.21 (0.55 – 2.67)	0.631	1.39 (0.70 – 2.75)	0.350
Food insecurity				
Secure	Ref.		Ref.	
Mild insecurity	0.88 (0.56 – 1.4)	0.596	1.15 (0.68 – 1.97)	0.599
Moderate insecurity	0.77 (0.47 – 1.25)	0.283	1.59 (1.01 – 2.51)	**0.044**
Severe insecurity	0.82 (0.53 – 1.26)	0.360	1.15 (0.78 – 1.71)	0.479
Maternal characteristics at enrollment:				
Marital status				
Married or cohabiting	Ref.		Ref.	
Previously married	0.67 (0.42 – 1.55)	0.104	0.95 (0.59 – 1.54)	0.839
Unemployed	1.20 (0.87 – 1.65)	0.264	1.35 (0.97 – 1.88)	0.071
Educational attainment				
Primary or below	Ref.		Ref.	
Secondary or higher	1.13 (0.82 – 1.55)	0.459	0.63 (0.45 – 0.89)	**0.009**
Parity				
Primiparous	Ref.		Ref.	
2-4	0.89 (0.47 – 1.66)	0.706	1.47 (1.02 – 2.13)	**0.037**
>4	0.95 (0.49 – 1.84)	0.876	1.55 (0.91 – 2.64)	0.106
Maternal depression at enrollment				
None	Ref.		Ref.	
Minimal to mild	0.98 (0.70 – 1.37)	0.905	1.37 (0.96 – 1.96)	0.087
Moderate to severe	1.42 (0.56 – 3.56)	0.457	2.71 (1.07 – 6.89)	**0.036**
ART started preconception	0.92 (0.61 – 1.37)	0.667		
DTG-based ART regimen	0.96 (0.58 – 1.60)	0.889		
Viral suppression (<1000 copies/mL)	0.70 (0.35 – 1.37)	0.296		
Infant characteristics:				
Female sex	0.90 (0.65 – 1.23)	0.508	0.85 (0.61 – 1.18)	0.322
Preterm delivery (<37 weeks' gestation)	0.52 (0.31 – 0.87)	**0.013**	1.13 (0.66 – 1.94)	0.644
Low birthweight (≤2500 grams)	1.15 (0.60 – 2.18)	0.674	0.54 (0.27 – 1.05)	0.071
Breastfeeding duration (days)	1.00 (1.00 – 1.00)	0.646	1.00 (1.00 – 1.00)	0.938

HR, Hazard Ratio; CI, Confidence Interval; Ref, Reference Category

Appendix Table 2 Covariates and risk of time to first episode of acute diarrhea in the first year of life by infant HIV-exposure status

	HIV-Exposed Uninfected		HIV-Unexposed	
	HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*
Household characteristics:				
Crowding (≥3 per room)	0.61 (0.18 – 2.05)	0.422	0.95 (0.39 – 2.29)	0.900
Household wealth*				
Middle-class to wealthy	Ref.		Ref.	
Poor to poorest	0.39 (0.15 – 1.00)	**0.049**	0.96 (0.46 – 2.02)	0.918
Food insecurity				
Secure	Ref.		Ref.	
Mild insecurity	1.39 (0.31 – 6.20)	0.669	1.38 (0.48 – 3.98)	0.548
Moderate insecurity	3.79 (1.02 – 14.00)	**0.046**	1.67 (0.69 – 4.04)	0.252
Severe insecurity	1.32 (0.31 – 5.53)	0.705	0.84 (0.34 – 2.10)	0.717
Maternal characteristics at enrollment:				
Marital status				
Married or cohabiting	Ref.		Ref.	
Previously married	1.48 (0.5 – 4.39)	0.480	2.49 (0.64 – 11.3)	**0.025**
Unemployed	0.53 (0.21 – 1.36)	0.188	1.16 (0.58 – 2.33)	0.676
Educational attainment				
Primary or below	Ref.		Ref.	
Secondary or higher	0.88 (0.38 – 2.06)	0.767	0.96 (0.47 – 1.99)	0.921
ART started preconception	5.39 (0.72 – 40.20)	0.100		
DTG-based ART regimen	2.74 (0.37 – 20.40)	0.324		
Viral suppression (<1000 copies/mL)	0.68 (0.16 – 2.91)	0.601		
Infant characteristics:				
Female sex	1.08 (0.47 – 2.50)	0.849	0.64 (0.32 – 1.31)	0.222
Preterm delivery (<37 weeks' gestation)	0.33 (0.04 – 2.43)	0.275	0.94 (0.29 – 3.09)	0.918
Breastfeeding duration (days)	1.00 (0.99 – 1.00)	0.182	1.00 (0.99 – 1.00)	0.366

**Comparison of upper 3 quintiles to lower 2 (middle class, wealthy, wealthiest vs. poor, poorest)*
HR, Hazard Ratio; CI, Confidence Interval; Ref, Reference Category

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