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C-Reactive Protein Independently Predicts HIV-related Outcomes among Women and Children in a Resource-Poor Setting

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Abstract

Objective—To evaluate C-reactive protein (CRP), an inflammatory marker, as a predictor of HIV-related outcomes among women and children in a resource-poor setting.

Design—We measured serum CRP concentration among 606 HIV-infected women, all of whom were not taking highly-active antiretroviral therapy, 3 to 11 months after they gave birth, and assessed relationships of CRP to HIV-related endpoints, including maternal disease progression, mother-to-child transmission of HIV, and maternal and child mortality.

Methods—We used Cox proportional hazards and logistic regression models adjusted for age, sociodemographic characteristics, anthropometric measurements, hemoglobin, CD4 cell count, HIV viral load, and, for child outcomes, breastfeeding status.

Results—Ninety-four women had a high CRP concentration (>10 mg/l). During the study follow-up, 56 women progressed to WHO stage 4 and 188 died, and a high maternal CRP concentration was significantly associated with a 2.26-fold (95% CI 1.64–3.12) greater risk of progression to stage 4 or death. Among children, 174 acquired HIV and 116 died by age 2 years,

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Author's Contributions

PKD and RK analyzed and interpreted the data, and PKD wrote the initial draft of the manuscript. WWF and GM are principal investigators of the Tanzania Vitamin Supplementation Trial and contributed to the study design and its implementation. FM contributed to the study implementation. All authors participated in the manuscript preparation and revision, and read and approved the final manuscript.

and a high maternal CRP concentration was associated with a 3.03-fold (95% CI 1.85–4.96) greater risk of child mortality. In multivariate analyses among adults, a high maternal CRP concentration was significantly associated with a 1.55-fold (95% CI 1.08–2.23) greater risk of progression to stage 4 or death. A maternal CRP concentration was not significantly associated with mother-to-child transmission of HIV.

Conclusions—A high maternal CRP concentration independently predicts HIV disease progression, maternal mortality, and child mortality in a resource-poor setting. C-reactive protein may be an important and inexpensive prognostic indicator for HIV-infected women and their children.

Keywords

C-reactive protein; HIV/AIDS; disease progression; mortality; mother-to-child transmission; resource-poor setting

Introduction

The cost of routinely monitoring CD4 T-cell lymphocytes and HIV plasma viral load are prohibitively high for many resource-poor settings, and less-expensive assays may be useful in these situations to guide HIV care and treatment [1]. C-reactive protein (CRP), an acute-phase response protein that increases in acute and chronic inflammatory disorders [2], has been shown to predict cardiovascular events among both individuals with angina and healthy physicians [3–5], and predict mortality among patients with pancreatic or colorectal cancer [6,7]. Increased CRP concentrations also predict mortality among HIV-negative immunocompromised patients with *Pneumocystis carinii* pneumonia [8].

Higher CRP concentrations have been associated with lower CD4 cell counts and higher HIV RNA levels among HIV-infected individuals [9], but results from studies evaluating serum CRP as a predictor of mortality in resource-rich settings are conflicting. Studies have reported significant associations between increased CRP concentrations and faster time to AIDS and greater risk of mortality, but did not use clinically established CRP cut-off concentrations [9–11]. A third study found that a clinically elevated CRP concentration was associated with a significant reduction in the risk of mortality [12]. While a prognostic indicator of HIV disease progression and mortality would be beneficial to all HIV clinicians, those working in resource-poor settings have a greater need for an inexpensive prognostic marker. Therefore, the objective of this study was to evaluate serum CRP as a predictor of adverse maternal and child HIV-related outcomes in a resource-poor setting.

Methods

Study Design

Starting in April 1995, 1,078 HIV-infected pregnant women were enrolled into a randomized trial of multivitamin supplementation in Dar es Salaam, Tanzania. The trial design has been described in detail [13]. In brief, women were provided daily multivitamins and followed, along with their child, until the end of the study in August 2003. In this sub study, we measured CRP concentration in stored frozen plasma samples obtained from 611

women. All samples had been collected within one year after the woman gave birth. None of the participants had received antiretroviral therapy during the study.

Laboratory Methods

Detailed laboratory methods of the parent study have been described [13]. In brief, we used Roche Amplicor version 1.5 assay to quantify HIV-1 RNA and Becton Dickinson FACScout or FACSCAN systems to quantify CD4 T-cell count. Plasma samples were then stored in a -70 Celsius freezer until 611, which had enough stored blood at the time of testing, were obtained for CRP testing. We used an immunoturbidimetric assay on a Hitachi 917 analyzer (Roche Diagnostics) using reagents and calibrators from Denka Seiken (Niigata, Japan) to determine the concentration of CRP in plasma. This assay had a sensitivity of 0.03 mg/l and day-to-day variability of 2.81, 1.61 and 1.1% at concentrations of 0.91, 3.07 and 13.38 mg/l, respectively. Among the 611 plasma samples tested, results were not available for four plasma samples that hemolyzed during laboratory testing.

Statistical Analyses

Among the 607 plasma samples with measured CRP concentrations, we excluded one sample for being obtained within one month of giving birth. Therefore, CRP concentrations from 606 HIV-positive women were used in the analyses. A clinically elevated CRP concentration has been established as >10 mg/l [2,14]. All analyses were conducted using SAS 9.1 [(SAS Institute, Cary, NC)].

We determined associations between high maternal CRP concentration (>10 mg/l), using those with CRP ≤ 10 mg/l as a reference group, and primary maternal and child HIV-related outcomes. In addition, primary outcomes were compared among quartiles of CRP concentration, using the lowest CRP quartile as the reference group. Clinical data (body mass index, mid-upper arm circumference, hemoglobin, CD4 cell count, and HIV viral load) were included in analyses if they were collected within 28 days of the CRP sample.

Methods for determining the predefined primary clinical and mortality outcomes have been described [15,16]. In brief, primary maternal outcomes were progression to WHO stage 4, mortality to AIDS-related causes, and mortality to any cause. Primary child outcomes were mortality by age 2 years and mother-to-child transmission of HIV by age 2 years.

Maternal characteristics were compared between women with normal (≤ 10 mg/l) and high (>10 mg/l) CRP concentrations using a two-sided t-test for continuous variables and a chi-square test for categorical variables. Kaplan-Meier curves were used to display maternal progression to stage 4 or death among women with a normal and high CRP concentration; curves were compared using the log-rank test. Relationships of CRP concentration with predefined primary HIV-related endpoints were assessed using Cox proportional hazards models for maternal outcomes and logistic regression models for child outcomes. Maternal endpoints were included only if they occurred after the CRP sample date, and child endpoints were included if they occurred before or after the CRP sample date and before the child reached age 2. Among the CRP quartiles, a test for trend was conducted using the median CRP concentration of each quartile (lowest quartile, median 0.34 mg/l, IQR 0.23–0.46 mg/l; 2nd quartile, median 1.14 mg/l, IQR 0.87–1.55 mg/l; 3rd quartile median 2.96

mg/l, IQR 2.38–3.89 mg/l; highest quartile, median 18.18 mg/l, IQR 7.53–41.90 mg/l). When combined maternal outcomes were examined, the first end point to occur was used in the model. Univariate models were adjusted for maternal age and vitamin trial regimen group. Multivariate models were adjusted for maternal age, vitamin trial regimen group, sociodemographic characteristics, anthropometric measurements, hemoglobin, CD4 cell count, HIV plasma viral load, and, for child outcomes, breastfeeding status. We used categories of CD4 count (<200, 200–399, 400–599, 600–799, 800 cells/ μ l) and viral load (<25,000, 25,000–49,999, 50,000 copies/ml) in multivariate models.

Results

Among this cohort of 606 HIV-positive women, the median CRP concentration was 1.95 mg/l [interquartile range (IQR) 0.63 to 5.17 mg/l]. Ninety-four (15.5%) women had a high CRP concentration. Serum samples for CRP measurement were obtained a mean (\pm standard deviation) of 210 (\pm 27) days after women gave birth, and there was no significant difference in the time from delivery to obtaining the serum sample between the two groups (Table 1). Women with a high CRP concentration were significantly less likely to be breastfeeding at the date of the CRP sample, and significantly more likely to have a body mass index <18.5 kg/m², a mid-upper arm circumference <22 cm, a hemoglobin <11 g/dl, and a CD4 count <200 cells/ μ l. Plasma viral load was not significantly different between the two groups.

Maternal Outcomes

Women were followed for a median of 63.2 months (IQR 49.5 to 71.5 months) from the CRP sample date, and 56 (9.5%) women progressed to WHO stage 4, 144 (26.2%) women died from an AIDS-related cause, and 188 (31.0%) women died from any cause. In Kaplan-Meier analyses, the median time to progression to stage 4 or death from any cause was 6.8 and 4.3 years among women with a normal and high CRP concentration, respectively (Figure 1). Women with a high CRP concentration experienced a significantly faster progression to stage 4 or death compared to women with a normal CRP concentration ($p=0.002$). The median time to progression to stage 4 or death was 6.8 and 5.2 years for women in the 2nd and highest CRP quartiles, respectively. Over 50% of the women in the lowest and 3rd CRP quartiles survived without progression to stage 4 during the follow-up period.

In univariate proportional hazard analyses, a high CRP concentration was associated with an increased risk of progression to stage 4, mortality from AIDS-related causes, mortality from any cause, progression to stage 4 or death from AIDS-related causes, and progression to stage 4 or death from any cause (Table 2). In multivariate analyses, women with a high CRP concentration had a 1.90 (95% CI 0.94–3.81) greater risk of progression to stage 4, a 1.42-fold (95% CI 0.94–2.12) greater risk of progression to stage 4 or death from AIDS-related causes, and a 1.55-fold (95% CI 1.08–2.23) greater risk of progression to stage 4 or death from any cause after accounting for CD4 count, HIV viral load, and other prognostic variables.

Higher quartiles of CRP concentration were also significantly associated with adverse maternal HIV-related outcomes (Table 3). In univariate analyses, the highest two CRP quartiles were significantly associated with all of the adverse maternal outcomes, except for progression to stage 4, when compared to the lowest CRP quartile. In multivariate analyses, women in the highest CRP quartile had a 2.49-fold (95% CI 1.07–5.81) greater risk of progression to stage 4, a 1.88-fold (95% CI 1.13–3.15) greater risk of progression to stage 4 or mortality from AIDS-related causes, and a 2.22-fold (95% CI 1.40–3.50) greater risk of progression to stage 4 or mortality from any cause.

In further multivariate analyses, CRP was not a significant predictor of progression to stage 4 or mortality from any cause when establishing the follow-up cut-off at one year after the CRP sample date (hazard ratio 1.80, 95% CI 0.66–4.89). However, CRP was a significant predictor of progression to stage 4 or mortality from any cause within two years of the CRP sample date (HR 2.14, CI 1.10–4.18), and within four years of the CRP sample date (HR 1.93, CI 1.27–2.95) despite adjusting for CD4 count, HIV viral load, and other prognostic variables.

Child Outcomes

Among children, 174 (31.4%) acquired HIV and 116 (20.6%) died from any cause before 2 years of age. In univariate analyses, children born to women with a high CRP concentration had a significantly greater risk of mortality, but not mother-to-child transmission of HIV, before 2 years of age (Table 2). In multivariate analyses, children born to women with a high CRP concentration did not have a significantly greater risk of becoming infected with HIV, but had a 3.03-fold (95% CI 1.85–4.96) greater risk of death before reaching 2 years of age.

Only the highest quartile of CRP concentration was significantly associated with child mortality before age 2 when compared to the lowest CRP quartile (Table 3). In multivariate analyses, the higher CRP quartiles were not predictive of child outcomes after adjusting for maternal CD4 count, HIV viral load, and other prognostic variables.

Discussion

In this cohort of HIV-infected women in a resource-poor setting, a clinically elevated CRP concentration was predictive of HIV disease progression and mortality, independent of anthropometric measurements, CD4 cell count, and plasma viral load. In addition, a high post-partum maternal CRP concentration was predictive of child mortality, but not HIV transmission, before the age of 2 years, independent of maternal anthropometric measurements, CD4 cell count, plasma viral load, and breastfeeding status at the time of the serum CRP measurement.

Few studies have examined CRP as a predictor of AIDS or mortality in HIV-infected patients. Among 474 HIV-infected adults in Baltimore/Washington D.C., those with a CRP concentration >2.3 mg/l were significantly more likely to develop clinical AIDS than those with a CRP < 1.2 mg/l when adjusting for CD4 cell count, plasma viral load and hemoglobin [9]. In another study, CRP concentrations > 4 mg/l were associated with a 1.93-fold (95% CI

1.12–3.30) greater risk of AIDS-related mortality after adjusting for lean body mass (measured by bioelectrical impedance analysis and adjusted for height) and CD4 cell count, but not HIV plasma viral load, among 129 HIV-positive males in France [10]. Another study found that slightly increased CRP concentrations (4.1–6.0 versus 4.0 mg/l), but not a clinically significant CRP concentrations (< 13.6 versus 4.0 mg/l), were associated with an increased risk of mortality when adjusting for age, body mass index, serum albumin, CD4 cell count, and HIV-1 RNA among 204 HIV-infected women in New York [11]. This study was limited by the use of a low sensitivity CRP assay. A study among 62 HIV-positive homosexual men with *Mycobacterium avium-intracellulare* (MAC) infection in Sweden found that patients with a clinically elevated CRP concentration (>10 mg/l) had a significantly longer mean survival (365 days) compared to patients with a normal CRP concentrations (180 days) [12]. Our study expands on these previous studies by having a larger sample size, by examining a clinically established cut-off value for CRP, by extending analyses to include maternal HIV disease progression and adverse child HIV-related outcomes, by quantifying CRP with a high sensitivity assay, and by determining associations in a resource-poor setting.

The clinical significance of a high CRP concentration may be not only in detecting an underlying opportunistic infection among HIV-positive patients, but also in assisting in the diagnosis of infections, particularly among patients with inconclusive chest radiographs [12]. C-reactive protein is a component of the innate immune system and may activate the complement system during infections [17]. In HIV-infected patients, CRP concentrations increase with a range of infections [12,18,19], including pneumococcal community-acquired pneumonia [20] and pulmonary tuberculosis [21]. Patients infected with *Pneumocystis carinii* pneumonia (PCP), *Toxoplasmosis*, MAC, and pulmonary tuberculosis have significantly lower increases in CRP concentration compared to patients infected with more common bacterial pathogens [12,19]. However, one study found no significant difference in CRP concentrations between HIV-positives infected with PCP versus a common bacterial-causing pneumonia [22]. While it appears that CRP increases are greatest in those with bacterial infections [23], clinical interpretations may need to be adjusted for patient with a very low CD4 count (<50 cell/ μ l), since they have been observed to mount a smaller CRP response to PCP infections [22].

Although CRP could simply be a marker for opportunistic infections or underlying disease, high circulating concentrations of CRP may contribute to promoting disease progression and increasing mortality among HIV-infected patients. The basic metabolic disturbances that lead to HIV-associated weight loss and wasting, such as gastrointestinal malabsorption, altered metabolism, and changes in protein production, appear to represent an adaptive response to a generalized inflammatory state [24–27]. Weight loss and wasting are strong independent predictors of HIV-related morbidity and mortality [10,28,29]. In addition, an inflammatory process may lead to depleted vitamin and mineral concentrations, which may in turn impact HIV disease progression. High CRP concentrations have been shown to be associated with depleted stores of several vitamins and minerals among HIV-negative [30–33] and HIV-positive [34,35] adults. Deficiencies of several vitamins and minerals have also been associated with disease progression and mortality among HIV-positive adults [35–37].

Whether CRP is a marker of infectious diseases or a contributor to metabolic disturbances, resolution of acute inflammation appears to be important for survival. Among an HIV-positive cohort being treated for a MAC infection, 42 patients who normalized CRP concentrations after treatment had a significantly longer median survival than the 20 patients who did not normalize CRP concentrations after treatment ($p=0.016$) [12].

We noted an association between high maternal CRP concentration and increased risk of child mortality. As described, high CRP may be a marker or cause of accelerated maternal HIV disease progression, which in turn may lead to deficient transfer of passive immunity and nutrients to the child. This may thus lower immune function among children and subsequently elevate the risk of mortality [38, 39]. Poor caring practices due to maternal morbidity or death is a plausible social explanation leading to poor child outcomes. A recent study found that HIV-exposed but HIV-uninfected children had an increased risk of mortality if their HIV-infected mothers had advanced disease, and the most common cause of infant mortality was pneumonia and/or sepsis [40].

In our laboratory in Tanzania, a CD4 count and an HIV viral load cost approximately US \$10 and \$40 per blood sample, respectively. Meanwhile, a CRP test costs approximately \$2 per blood sample. Thus, a CRP test is approximately one-fifth the cost of a CD4 count and one-twentieth the cost of a HIV viral load. In our multivariate analyses, a high CRP was better than either CD4 count <200 and viral load $>50,000$ copies for predicting maternal disease progression to Stage 4. C-reactive protein was not better than CD4 count or viral load in predicting maternal mortality outcomes, but CRP remained a very strong and almost comparable predictor. In addition, a high CRP was better than viral load $>50,000$ copies for predicting child mortality before age two. Therefore, CRP may at least be a better and less expensive marker of maternal HIV disease progression and child mortality before age two, as compared to CD4 count or HIV viral load, in this resource-poor setting.

Our study population included women and children who were not taking antiretroviral therapy, and to our knowledge no studies have assessed CRP concentrations as a predictor of adverse HIV-related outcomes among people taking highly-active antiretroviral therapy (HAART). Few studies have examined the differences and longitudinal changes of CRP concentrations among HIV-infected patients taking antiretroviral therapy. One cross-sectional study found no significant difference in CRP concentrations between HIV-positive adolescents taking and not taking antiretroviral therapy [41]. Two longitudinal studies have suggested that antiretroviral therapy may significantly increase CRP concentrations despite expected immunologic and virologic responses [42,43]. These studies indicate that an inflammatory state may persist after the introduction of antiretroviral therapy and may continue to increase the risk of HIV-associated morbidity and mortality in the post-HAART era.

In conclusion, these results demonstrate that CRP is an independent predictor of adverse maternal and child HIV-related outcomes among HIV-positive mothers not taking antiretroviral therapy in a resource-poor setting. Future studies should assess associations between intrapersonal longitudinal changes in CRP concentrations and risks of adverse HIV-related outcomes, and evaluate associations between a high CRP concentration and risks of

adverse maternal and child HIV-related outcomes among patients taking HAART. Whether CRP is simply a marker of disease or part of the disease process itself, CRP may be an important and inexpensive prognostic indicator for HIV-infected patients, particularly in resource-poor settings.

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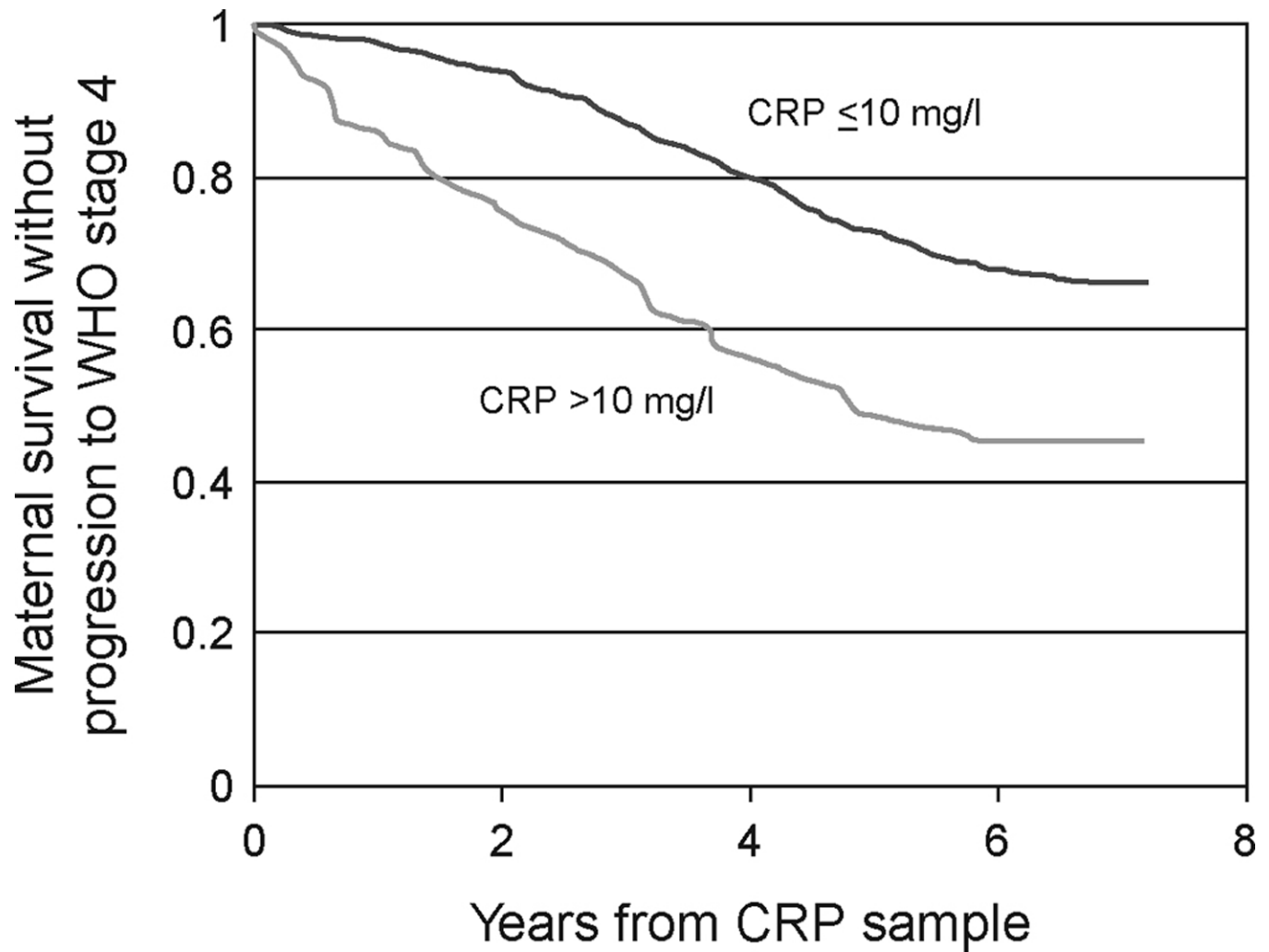


Figure 1.

Kaplan-Meier curve of survival without progression to WHO stage 4 among 588 HIV-infected women with a normal (≤ 10 mg/l) or high (>10 mg/l) C-reactive protein (CRP) concentration.

Table 1

Maternal characteristics stratified by normal (≤ 10 mg/l) versus high (>10 mg/l) C-reactive protein concentration among 606 HIV-infected women.

	CRP ≤ 10 N (%)	CRP > 10 N (%)	p-value ¹
Time from delivery to C-reactive protein sample (days) ²	210 \pm 26	209 \pm 36	0.72
Maternal age at recruitment <25 years	268 (52)	46 (49)	0.54
Gestational age at randomization <20 weeks	181 (35)	39 (41)	0.26
Mother has primary school education	459 (90)	87 (93)	0.39
Spending <500 TSh on food per household member per day	182 (40)	42 (48)	0.16
Still breastfeeding at date of CRP sample	426 (92)	66 (81)	0.003
Body Mass Index <18.5 kg/m ²	50 (10)	25 (27)	<0.0001
Mid-Upper Arm Circumference <22 cm	30 (6)	24 (26)	<0.0001
Hemoglobin <11 g/dl	220 (45)	59 (67)	<0.0001
CD4 <200 cells/ μ l	38 (8)	15 (17)	0.005
Viral load $>50,000$ copies/ml	39 (35)	8 (44)	0.43

CRP – C-reactive protein.

¹ Statistical analyses conducted using t-tests for continuous data and Chi-squared for categorical data.

² Mean \pm standard deviation.

Table 2

Association between maternal C-reactive protein concentrations (modeled > 10 mg/l) and adverse maternal and child HIV-related outcomes.¹

Outcomes	Maternal CRP (mg/l)	No. of Events/ No. at Risk (%)	Age-adjusted Model ²		Multivariate Model ³	
			Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Maternal Outcomes						
Progression to stage 4	10	45/498 (9%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	11/90 (12%)	1.99 (1.03–3.86)	0.04	1.90 (0.94–3.81)	0.07
Death from AIDS-related causes	10	111/512 (22%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	31/94 (33%)	1.88 (1.26–2.81)	0.002	1.00 (0.63–1.59)	0.99
Death from any cause	10	147/512 (29%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	41/94 (44%)	1.88 (1.33–2.66)	0.0004	1.19 (0.80–1.77)	0.38
Progression to stage 4 or death from AIDS-related causes	10	136/498 (27%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	39/90 (43%)	2.23 (1.56–3.19)	<0.0001	1.42 (0.94–2.12)	0.10
Progression to stage 4 or death from any cause	10	168/498 (34%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	49/90 (54%)	2.26 (1.64–3.12)	<0.0001	1.55 (1.08–2.23)	0.02
Child Outcomes						
Mother to child transmission of HIV by age 2	10	145/470 (31%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	29/85 (34%)	1.17 (0.71–1.91)	0.54	0.84 (0.47–1.50)	0.56
Death from any cause by age 2	10	82/475 (17%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	34/89 (38%)	3.03 (1.85–4.96)	<0.0001	1.70 (0.86–3.34)	0.13
Mother to child transmission HIV or death from any cause by age 2	10	172/475 (36%)	1.00 (Reference)	--	1.00 (Reference)	--
	>10	43/89 (48%)	1.66 (1.05–2.62)	0.03	0.94 (0.53–1.67)	0.83

CRP – C-reactive protein.

¹ Maternal outcomes assessed using Cox proportional hazard models and child outcomes assessed using logistic regression models.

² Univariate models adjusted for maternal age <25 years and vitamin trial regimen group.

³ Multivariate models adjusted for maternal age <25 years, vitamin trial regimen cohort, gestational age <20 weeks at enrollment, maternal education primary school, spending <500 TSh on food per day, BMI <18.5 kg/m², middle upper arm circumference <22 cm, hemoglobin <11 g/dl, CD4 count categories (<200, 200–399, 400–599, 600–799, 800) cells/μl, and viral load categories (<25,000, 25,000–49,999, 50,000) copies/ml. Analyses for child outcomes were additionally adjusted for breastfeeding status at date of CRP sample (yes/no).

Table 3

Risk of adverse maternal and child outcomes among 606 HIV-infected women by C-reactive protein quartiles.¹

Outcome	Maternal Quartile of CRP	No. of Events/ No. at Risk (%)	Age-adjusted model ²		Multivariate model ³		
			Hazard Ratio (95% CI)	P value for trend ⁴	Hazard Ratio (95% CI)	P value for trend ⁴	
Maternal Outcome							
Progression to stage 4	Lowest quartile	13/146 (9%)	1.00 (Reference)	--	1.00 (Reference)	--	0.15
	2 nd quartile	11/150 (7%)	0.92 (0.41–2.06)	0.84	1.04 (0.42–2.62)	0.92	
	3 rd quartile	17/146 (12%)	1.59 (0.77–3.28)	0.21	1.80 (0.81–3.96)	0.15	
	Highest quartile	15/146 (10%)	1.70 (0.80–3.61)	0.17	2.49 (1.07–5.81)	0.04	
Death from AIDS-related Causes	Lowest quartile	24/150 (16%)	1.00 (Reference)	--	1.00 (Reference)	--	0.67
	2 nd quartile	39/153 (25%)	1.74 (1.04–2.90)	0.03	2.21 (1.26–3.88)	0.006	
	3 rd quartile	37/151 (25%)	1.74 (1.04–2.91)	0.04	1.85 (1.04–3.27)	0.04	
	Highest quartile	42/152 (28%)	2.25 (1.36–3.73)	0.002	1.35 (0.74–2.46)	0.33	
Death from any cause	Lowest quartile	33/150 (22%)	1.00 (Reference)	--	1.00 (Reference)	--	0.29
	2 nd quartile	47/153 (31%)	1.52 (0.97–2.37)	0.07	1.98 (1.22–3.21)	0.006	
	3 rd quartile	48/151 (32%)	1.63 (1.04–2.54)	0.03	1.64 (0.99–2.70)	0.05	
	Highest quartile	60/152 (39%)	2.32 (1.51–3.56)	0.0001	1.73 (1.05–2.86)	0.03	
Progression to stage 4 or death from AIDS-related causes	Lowest quartile	32/146 (22%)	1.00 (Reference)	--	1.00 (Reference)	--	0.23
	2 nd quartile	44/150 (29%)	1.47 (0.93–2.32)	0.10	1.85 (1.10–3.08)	0.02	
	3 rd quartile	47/146 (32%)	1.75 (1.11–2.75)	0.02	2.01 (1.23–3.28)	0.006	
	Highest quartile	52/146 (36%)	2.32 (1.49–3.63)	0.0002	1.88 (1.13–3.15)	0.02	
Progression to stage 4 or death from any cause	Lowest quartile	39/146 (27%)	1.00 (Reference)	--	1.00 (Reference)	--	0.02
	2 nd quartile	51/150 (34%)	1.39 (0.91–2.11)	0.13	1.78 (1.12–2.83)	0.02	
	3 rd quartile	58/146 (40%)	1.74 (1.16–2.61)	0.008	1.87 (1.20–2.93)	0.006	
	Highest quartile	69/146 (47%)	2.49 (1.68–3.71)	<0.0001	2.22 (1.40–3.50)	0.0007	
Child Outcome							
Mother to child transmission of HIV by age 2	Lowest quartile	41/135 (30%)	1.00 (Reference)	--	1.00 (Reference)	--	0.11
	2 nd quartile	39/141 (28%)	0.86 (0.51–1.46)	0.58	0.82 (0.46–1.46)	0.50	
	3 rd quartile	51/141 (36%)	1.25 (0.75–2.09)	0.39	1.19 (0.67–2.13)	0.55	

Outcome	Maternal Quartile of CRP	No. of Events/ No. at Risk (%)	Age-adjusted model ²		Multivariate model ³	
			Hazard Ratio (95% CI)	P value for trend ⁴	Hazard Ratio (95% CI)	P value for trend ⁴
Death from any cause by age 2	Highest quartile	43/138 (31%)	1.07 (0.64–1.81)	0.79	0.62 (0.33–1.16)	0.14
	Lowest quartile	25/137 (18%)	1.00 (Reference)	--	1.00 (Reference)	--
	2 nd quartile	23/142 (16%)	0.84 (0.45–1.59)	0.60	1.33 (0.54–3.28)	0.54
	3 rd quartile	26/143 (18%)	0.99 (0.53–1.83)	0.97	1.01 (0.40–2.51)	0.99
Mother to child transmission of HIV or death from any cause by age 2	Highest quartile	42/142 (30%)	1.92 (1.08–3.41)	0.03	1.26 (0.57–2.80)	0.57
	Lowest quartile	50/137 (37%)	1.00 (Reference)	--	1.00 (Reference)	--
	2 nd quartile	47/142 (33%)	0.84 (0.51–1.39)	0.50	0.93 (0.52–1.66)	0.81
	3 rd quartile	59/143 (41%)	1.22 (0.75–1.98)	0.44	1.16 (0.66–2.06)	0.60
	Highest quartile	59/142 (42%)	1.28 (0.78–2.08)	0.33	0.68 (0.37–1.26)	0.22

CRP - C-reactive protein.

Range of CRP concentration (mg/l) by quartile: lowest quartile (0.02–0.62), 2nd quartile (0.63–1.94), 3rd quartile (1.95–5.16), highest quartile (5.17–351.6).

¹ Maternal outcomes assessed using Cox proportional hazard models and child outcomes assessed using logistic regression models.

² Univariate models adjusted for maternal age <25 years and vitamin trial regimen group.

³ Multivariate models adjusted for maternal age <25 years, vitamin trial regimen cohort, gestational age <20 weeks at enrollment, maternal education primary school, spending <500 TSh on food per day, BMI <18.5 kg/m², middle upper arm circumference <22 cm, hemoglobin <11 g/dl, CD4 count categories (<200, 200–399, 400–599, 600/799, 800) cells/μl, and viral load categories (<25,000, 25,000–49,999, 50,000) copies/ml. Analyses for child outcomes were additionally adjusted for breastfeeding status at date of CRP sample (yes/no).

⁴ P value for trend among CRP quartile medians (lowest quartile 0.335, 2nd quartile 1.14, 3rd quartile 2.96, highest quartile 18.175).