Hyponatremia, Hypochloremia, and Hypoalbuminemia Predict an Increased Risk of Mortality during the First Year of Antiretroviral Therapy among HIV-infected Zambian and Kenyan Women

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ABSTRACT (word count: 246)

Background: Early mortality rates after initiating antiretroviral therapy (ART) are high in sub-Saharan Africa. We examined whether serum chemistries at ART initiation predicted mortality among HIV-infected women.

Methods: From May 2005-January 2007, we enrolled women initiating ART in a prospective cohort study in Zambia and Kenya. We used Cox proportional hazards models to identify risk factors associated with mortality.

Results: Among 661 HIV-infected women, 53 (8%) died during the first year of ART, and tuberculosis was the most common cause of death (32%). Women were more likely to die if they were both hyponatremic (sodium < 135 mmol/L) and hypochloremic (chloride < 95 mmol/L) (37% vs. 6%) or hypoalbuminemic (albumin < 34 g/L, 13% vs. 4%) when initiating ART. A body mass index < 18 kg/m^2 (adjusted hazard ratio [aHR] 5.3, 95% confidence interval [CI] 2.6-10.6) and hyponatremia with hypochloremia (aHR 4.5, 95% CI 2.2-9.4) were associated with one-year mortality after adjusting for country, CD4 cell count, WHO clinical stage, hemoglobin, and albumin. Among women with a CD4 cell count >50 cells/μL, hypoalbuminemia was also a significant predictor of mortality (aHR = 3.7, 95% CI 1.4 – 9.8)

Conclusions: Baseline hyponatremia with hypochloremia and hypoalbuminemia predicted mortality in the first year of initiating ART, and these abnormalities might reflect opportunistic infections (e.g., tuberculosis) or advanced HIV disease. Assessment of serum sodium, chloride, and albumin can identify HIV-infected patients at highest risk for mortality who may benefit from more intensive medical management during the first year of ART.

Introduction

Access to antiretroviral therapy (ART) in Africa has expanded rapidly, with an increase in the estimated number of people receiving treatment from 100,000 in 2003 to 2.9 million by December 2008 [1]. Although increased ART coverage has led to substantial declines in mortality, mortality rates, especially during the first year after ART initiation, remain higher in African countries compared with higher-income countries [2]. Mortality rates of HIV-infected adults initiating ART in Africa have ranged from 8 to 16 deaths per 100 person-years [3-7]. Established predictors of mortality in low-income settings include indicators of advanced HIV infection (i.e., low CD4 cell count and WHO clinical stage 4 disease), low hemoglobin, low body mass index (BMI), and certain opportunistic infections (e.g., tuberculosis) [3;4;6-10]. Several interventions have been proposed to reduce mortality in low-income settings, including promotion of earlier HIV diagnosis, treatment adherence support, and optimal prevention, screening, and management of opportunistic infections [11].

Accurate identification of risk factors for mortality is a critical step towards reducing mortality in low-income settings. Ideally, we want to identify risk factors that: (1) accurately predict mortality; (2) can be easily evaluated; and (3) indicate potentially treatable clinical problems. Although serum electrolyte and protein abnormalities are common with HIV-infection and may be associated with mortality, these abnormalities are rarely tested for in low-income settings [12-16]. In 2008, many African countries adopted the Maputo Declaration on Strengthening of Laboratory Systems, and several countries, including Zambia and Kenya, have taken steps to improve laboratory capacity [17]. In addition, WHO-AFRO has developed a pragmatic, stepwise laboratory accreditation process with quality assurance, quality control, and quality improvement programs that is being implemented in more than 10 African countries [18]. Increasingly, HIV-infected patients in these settings receive liver and renal

function tests prior to initiating ART [19]. This testing is performed by automated chemistry analyzers that can simultaneously perform multiple biochemical assays including tests for serum electrolytes and protein. We explored the use of serum electrolytes and protein measures as predictors of mortality in a prospective, observational cohort of HIV-infected Zambian and Kenyan women initiating ART.

Methods

We explored risk factors for death among women who had enrolled in the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Response Study, a prospective observational cohort study to evaluate the effectiveness of NNRTI-based ART in women previously exposed to a single intrapartum dose of nevirapine [20]. Women were enrolled from clinics in Lusaka, Zambia; Nairobi, Kenya; and Bangkok, Thailand during May 2005-January 2007. We limited this analysis to women from Zambia and Kenya. Women aged 18 years or older who met criteria to start ART according to national guidelines were eligible to participate in the study. In Zambia and Kenya, eligibility criteria to start ART included: CD4 cell count < 200 cells/μL, WHO stage 4 disease, or WHO stage 3 disease with CD4 cell count < 350 cells/μL. First-line ART regimens included nevirapine or efavirenz plus lamivudine with either stavudine or zidovudine. Written informed consent to participate in this study was obtained from each participant in her preferred language: English, Nyanja (Zambia), Bemba (Zambia), or Kiswahili (Kenya). Institutional review boards of the University of Zambia's Research Ethics Committee, the University of Alabama at Birmingham, the University of Nairobi/Kenyatta National Hospital, and CDC all reviewed and approved this study.

Women were followed for up to one year. Medical care was delivered by non-physician clinicians supervised by physicians. Throughout the study period, information on deaths was

collected using standardized forms. Deaths were reported by community health workers, heath care providers, or family members. The cause of death and associated clinical details were abstracted from medical records and death certificates and through verbal communications with family members.

Clinical and laboratory data

At enrollment, study participants received a medical history and physical examination, an evaluation for tuberculosis co-infection, and baseline laboratory testing that included CD4 cell count, HIV-1 RNA viral load, a complete blood count, and serum chemistries (sodium, potassium, chloride, creatinine, alanine transferase [ALT], aspartate transaminase [AST], and albumin) [20].

Baseline laboratory data were categorized according to National Institutes of Health Division of Acquired Immune Deficiency Syndrome (DAIDS) grades for severity of adult adverse events [21]. Baseline hemoglobin results were categorized as < 8 g/dL, 8 – 10 g/dL, or > 10 g/dL. Creatinine clearance was calculated using the Cockcroft-Gault equation, and we dichotomized renal function at 50 mL/min. Since the concentrations of electrolytes are tightly regulated and in balance with each other, electrolyte results are usually interpreted in the context of other electrolyte results. We created a four-level variable to assess baseline levels of sodium and chloride together: (1) normal sodium (> 135 mmol/L) and chloride levels (> 95 mmol/L); (2) normal sodium with hypochloremia (chloride levels ≤ 95 mmol/L); (3) hyponatremia (sodium levels ≤ 135 mmol/L) with normal chloride; and (4) hyponatremia with hypochloremia. We also collapsed this variable into two categories: (a) normal sodium or chloride (groups 1, 2, and 3) or (b) hyponatremia with hypochloremia (group 4).

Statistical analysis

All data were analyzed using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC). We compared baseline patient demographics, clinical findings, and laboratory results among women who died with women not known to have died. Among women who presented with hyponatremia with hypochloremia, we compared demographic and clinical characteristics by survival outcome. For all analyses, we compared categorical variables using the chi-squared test or Fisher's exact test and continuous variables using the Wilcoxon rank sum test; p-values < 0.05 were considered statistically significant.

We assessed associations between baseline patient demographics, clinical findings, and laboratory results, with morality during the first year after initiation of ART using Kaplan-Meier survival methods with corresponding log-rank tests and Cox proportional hazards models. Women lost to follow-up or who withdrew from the study were censored at the date of their last study visit. One Kenyan woman who died in a road traffic accident was censored at the date of her death. We included variables with a log-rank p-value < 0.1 in a multiple Cox proportional hazards model. We used backwards elimination to find the best fitting model. In the final model, we made an *a priori* decision to include the variables for country and several established risk factors for HIV-associated mortality, including BMI, WHO clinical stage, CD4 cell count, and hemoglobin [3;4;6;7]. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated for all variables in the final model. We also tested certain variables for interactions (e.g., sodium and albumin; albumin and CD4 cell count) based on previous literature [22;23] and when interactions were detected, stratified models were performed.

Results

Baseline patient characteristics.

NNRTI-based ART was initiated in 661 women (509 Zambian and 152 Kenyan). Women enrolled in the study had moderate to advanced immunosuppression as evidenced by a median CD4 cell count of 147 cells/μL (interquartile range [IQR]: 85 – 211). Zambian and Kenyan women had similar median age, BMI, CD4 cell count and WHO clinical stage but differed by baseline HIV viral load, hemoglobin, sodium, chloride, and albumin concentrations (Table 1). Overall, 268 (41%) women had at least one established risk factor for early mortality at study enrollment including: 162 (25%) women with a low baseline BMI (< 18 kg/m^2), 90 (14%) with a baseline CD4 cell count < 50 cells/μL, 61 (9%) with WHO clinical stage 4 disease, and 48 (7%) with a baseline hemoglobin < 8 g/dL. At baseline, 304 (46%) women had hyponatremia, 56 (8.5%) women had hypochloremia, 38 (6%) women had hyponatremia with hypochloremia, and 255 (39%) women had hypoalbuminemia (albumin < 34 g/L).

Patient outcomes and causes of death.

Of 661 women enrolled, 576 (87%) were alive and continuing in care after one year of ART, 32 (5%) women were lost to follow-up or withdrew, and 53 (8%) died, of whom 36 (68%) died during the first three months of ART. Compared with women known to have survived one year after initiation of ART, women who were lost to follow up or withdrew did not differ by BMI, WHO stage, CD4 cell count, or HIV viral load at enrollment (data not shown). The causes of death included tuberculosis (32%), diarrhea/dehydration (9%), pneumonia (7%), meningitis (7%), malaria (4%), other causes (17%), and unknown causes (23%) during the first year of ART. Only 2 (11%) of the 17 women who died of tuberculosis during follow-up had been diagnosed with active tuberculosis at baseline. Conversely, 7 (13%) of

the 56 women with a diagnosis of tuberculosis at baseline died during the first year of ART; causes included tuberculosis (n=2), pneumonia (n=2), fever (n=1), and unknown (n=2).

Risk factors for mortality within the first year of ART initiation.

In single-predictor analysis, the risk of death was significantly higher for women with low BMI, WHO stage 4 disease, CD4 cell count < 50 cells/μL, HIV viral load ≥ 100,000 copies/mL, or hemoglobin < 10 g/dL at baseline (Table 2). Baseline tuberculosis co-infection was not significantly associated with a higher risk of death. The probability of survival did not differ by country or age. Women with a baseline platelet count < 125 x 10^3/L, creatinine clearance < 50 mL/min, abnormal transaminases, hypochloremia, or hypoalbuminemia also had a significantly higher risk of death (Table 2).

By Kaplan-Meier survival methods, we assessed the association of sodium and chloride levels using the four-level variable described. We found that women who presented with hyponatremia and hypochloremia at ART initiation had a significantly lower probability of survival at one year (0.58, 95% CI 0.37-0.75) compared with women with either normal sodium and chloride levels (0.94), normal sodium with hypochloremia (0.94), or hyponatremia with normal chloride (0.94). Given the similar probabilities of survival in the later three groups, in further analysis, we compared women who had hyponatremia and hypochloremia with the combined group of women who had either a normal sodium or chloride level at ART initiation (Figure 2). In a Cox proportional hazards model, women with both hyponatremia and hypochloremia had 7.8 times (95% CI: 4.1 – 14.5) the risk of death compared with women who had either a normal sodium or chloride level at baseline (Table 2). In a multiple-predictor Cox proportional hazards model, low BMI (aHR = 5.3, 95% CI 2.6 – 10.6) and hyponatremia with hypochloremia (aHR = 4.5, 95% CI 2.2 – 9.4)

remained significant predictors of increased risk of death during the first year after ART initiation (Table 2). Other baseline results (i.e., platelet count < 125 x 10^3/L, creatinine clearance < 50 mL/min, abnormal transaminases) did not remain significant predictors of mortality in this multiple-predictor model.

Among 38 women with hyponatremia and hypochloremia at baseline, we did not detect differences among these women who died and survived in the median sodium (128 vs. 124; p=0.38) and chloride (91 vs. 92; p=0.89) levels respectfully. Tuberculosis was the cause of death in 7 (50%) of 14 hyponatremic and hypochloremic women who died compared with 10 (26%) of 39 women who died but were not hyponatremic and hypochloremic. None of the hyponatremic and hypochloremic women who died of tuberculosis were diagnosed with tuberculosis infection at baseline.

Hypoalbuminemia was associated with an increased risk of death in the single predictor model but not in the multiple predictor model (Table 2). In our analysis of potential interactions, however, we identified a possible interaction between albumin and CD4 cell count. We examined the association of hypoalbuminemia on mortality stratified by baseline CD4 cell count. Among women with a CD4 cell count >50 cells/μL, hypoalbuminemia was a significant predictor of mortality as 24 (12%) of 208 women with hypoalbuminemia died compared with 7 (2%) of 328 women with normal albumin (HR 5.7, 95% CI 2.5 – 13.3). Among women with a CD4 cell count < 50 cells/μL, however, hypoalbuminemia was not associated with mortality as 9 (19%) of 47 women with hypoalbuminemia died compared with 8 (20%) of 40 with normal albumin (HR 1.0, 95% CI 0.4 – 2.5). In a multiple-predictor Cox proportional hazards model stratified by CD4 cell count, hypoalbuminemia remained a significant predictor of mortality among women with a CD4 cell count >50 cells/μL (aHR =

3.7, 95% CI 1.4 – 9.8) and was not associated with mortality among women with a CD4 cell count < 50 cells/μL (aHR = 0.5, 95% CI 0.2 – 1.7) after adjusting for country, BMI, WHO clinical stage, hemoglobin, and hyponatremia with hypochloremia.

Discussion

In this cohort of HIV-infected Zambian and Kenya women initiating ART, we observed an overall mortality rate of 8% during the first year of treatment. The majority of deaths occurred within the first three months of ART initiation, and tuberculosis was the most common cause of death. Low BMI, hyponatremia with hypochloremia, and hypoalbuminemia (among women with a CD4 cell count >50 cells/μL) were independently associated with one-year mortality. In addition to established risk factors for mortality (e.g., CD4 cell count, WHO clinical stage of disease, hemoglobin), electrolyte and protein abnormalities may provide important prognostic information to help identify patients who are at the highest risk of death after initiating ART.

Hyponatremia is a common electrolyte abnormality among HIV-infected adults with advanced HIV disease [15;16]. Common causes of hyponatremia in HIV-infected patients include the syndrome of inappropriate antidiuretic hormone (SIADH), gastrointestinal fluid loss (e.g. diarrhea), adrenal insufficiency, and renal failure [24-26]. Serum chloride and sodium levels are closely regulated together and conditions that result in hyponatremia can also cause hypochloremia. Notably, we observed a much higher rate of mortality among women with both hyponatremia and hypochloremia compared with women who only had one electrolyte abnormality. This observation suggests that combined hyponatremia and hypochloremia may reflect a more profound and clinically concerning electrolyte disturbance in HIV-infected patients. Many hyponatremic and hypochloremic women in our cohort also had low CD4

cell counts and low BMI, but few patients reported diarrheal symptoms at study enrollment, and few women had baseline renal insufficiency. SIADH can be caused by a variety of conditions including malignant diseases (e.g., lung cancer), pulmonary disorders (e.g., tuberculosis and bacterial pneumonia), disorders of the central nervous system (e.g., meningitis, intracranial masses, bleeding), and certain drugs [27]. By disturbing ADH homeostasis, these illnesses lead to inappropriate retention of water, but not sodium, at the kidney's distal tubule and collecting duct, thus generating hyponatremia.

In this cohort of women, the prevalence of hyponatremia was high at ART initiation, but few women had profoundly low sodium concentrations (< 124 mmol/L). This observation suggests that subsequent mortality may have resulted from undiagnosed conditions underlying these electrolyte disturbances and not from the electrolyte abnormality itself. For example, a large proportion of women who presented with hyponatremia and hypochloremia at ART initiation subsequently died of tuberculosis that was not clinically detected at study enrollment. Both pulmonary and extrapulmonary (e.g., tuberculous meningitis) tuberculosis can cause SIADH [28;29]. Tuberculosis can be difficult to diagnose in HIV-infected patients in resource-limited settings as a high proportion of these patients have negative sputum smears and can only be diagnosed with liquid mycobacterial culture media, which are often not available [30]. Even in areas with high rates of tuberculosis and high rates of empiric tuberculosis therapy, a significant proportion of deaths among HIV-infected patients are due to unsuspected tuberculosis [31]. The detection of hyponatremia with hypochloremia in HIV-infected patients initiating ART might indicate the presence of tuberculosis or other lung and central nervous system infections (e.g., cryptococcal meningitis) that may not be clinically apparent. Therefore, screening for low sodium and chloride levels at the start of ART could improve HIV-infected patient outcomes if coupled with additional diagnostic tests (i.e., liquid

mycobacterial culture, serum cryptococcal antigen testing) and treatment for opportunistic infections.

Hypoalbuminemia was also associated with a higher risk of death within the first year after initiating ART among women with higher CD4 cell counts (> 50 cells/μL). Hypoalbuminemia has been previously shown to be a predictor of mortality among a cohort of HIV-infected women in the United States and among HIV-infected patients initiating ART in London [14;22]. The etiology of hypoalbuminemia in HIV infection is often multi-factorial and could indicate malnutrition, chronic inflammation due to advanced HIV infection, wasting syndrome, enteropathy, or liver disease (e.g. chronic hepatitis B virus co-infection) [13;22]. Hypoalbuminemia was not predictive of mortality among women with low CD4 cell counts (< 50 cells/μL) and this observation may have resulted from a plateau effect as women with a low CD4 cell count already have a high risk of mortality (20%). Of interest, this interaction between albumin and CD4 cell count has also been observed among HIV-infected women in the US [22].

Electrolyte and protein abnormalities are rarely tested for in low-income settings because of limited laboratory capacity. In recent years, however, laboratory systems have improved substantially in several African countries and increasing numbers of HIV-infected patients have access to clinical chemistry testing [1;19]. Additionally, clinics that have integrated laboratory monitoring into patient care, such as those in Zambia and Kenya, have invested in high throughput automated chemistry analyzers that increase efficiency [32]. Adding testing for electrolytes and albumin in these settings would be relatively inexpensive, and evaluating the benefits of these tests prospectively is warranted.

The results of this study are subject to several limitations. First, our study was conducted among women in Zambia and Kenya and may not be generalizable to other populations. Second, clinics applied their own algorithms to screen for active tuberculosis infection, which could have led to differential ascertainment of disease and possible misclassification. We also do not have other data on underlying conditions, such as cryptococcal antigenemia, that could have affected one-year mortality and contributed to the prevalence of hyponatremia among these women [33;34]. Finally, we were unable to measure urine sodium concentrations and urine osmolality to confirm the contribution of SIADH to hyponatremia in this study.

In summary, this study demonstrated that the presence of electrolyte (hyponatremia and hypochloremia) and protein (hypoalbuminemia) abnormalities at ART initiation were important predictors of mortality during the first year of treatment in these low-income settings. In addition to routine clinical and laboratory monitoring, specific assessment of sodium, chloride, and albumin might help clinicians identify patients at the highest risk for mortality possibly due to undiagnosed opportunistic infections. A prospective study should evaluate whether testing for sodium, chloride, and albumin combined with additional diagnostic tests for opportunistic infections can reduce mortality in HIV-infected patients initiating ART in low-income settings.

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Table 1: Baseline characteristics of HIV-infected Zambian and Kenyan women initiating antiretroviral therapy in the NNRTI Response Study (n=661), 2005 – 2007

	Zambia n = 509	Kenya n = 152	p-value
Age, years	32 (28-36)	32 (28-36)	0.68
Body mass index (BMI), kg/m^2	19.7 (18.3-21.9)	19.9 (17.7-22.6)	0.74
CD4 cell count, cells/μL	148 (88-211)	147 (77-212)	0.51
HIV plasma viral load, copies/mL*	94,000 (26,400–272,000)	214,205 (62,995- > 750,000)	< 0.01
WHO stage			0.08
I or II	215 (42)	61 (40)	
III	254 (50)	70 (46)	
IV	40 (8)	21 (14)	
Diagnosis of active tuberculosis			0.77
No	465 (91)	140 (92)	
Yes	44 (9)	12 (8)	
Hemoglobin*, g/dL	10.8 (9.6-12.0)	10.4 (8.8-12.0)	0.01
Sodium*, mmol/L	135 (132-137)	139 (136-142)	<0.01
Chloride*, mmol/L	103 (101-105)	98 (95-100)	< 0.01
Albumin*, g/L	34 (30-38)	40 (34-49)	< 0.01

Data presented are no. (%) or median (interquartile range, IQR)

* Baseline hemoglobin results was missing for 16 participants; baseline sodium and chloride results were missing for 57 participants; and baseline albumin results were missing for 38 participants.

Table 2: Risk factors for mortality during the first year of antiretroviral therapy among HIV-infected Zambian and Kenyan women (n=661), 2005 – 2007

	Died N=53	Not known to have died N=608*	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)†
Country				
Zambia	35 (7)	474 (93)	1.0	
Kenya	18 (12)	134 (88)	1.7 (1.0-3.0)	1.1 (0.5-2.2)
Age, years				

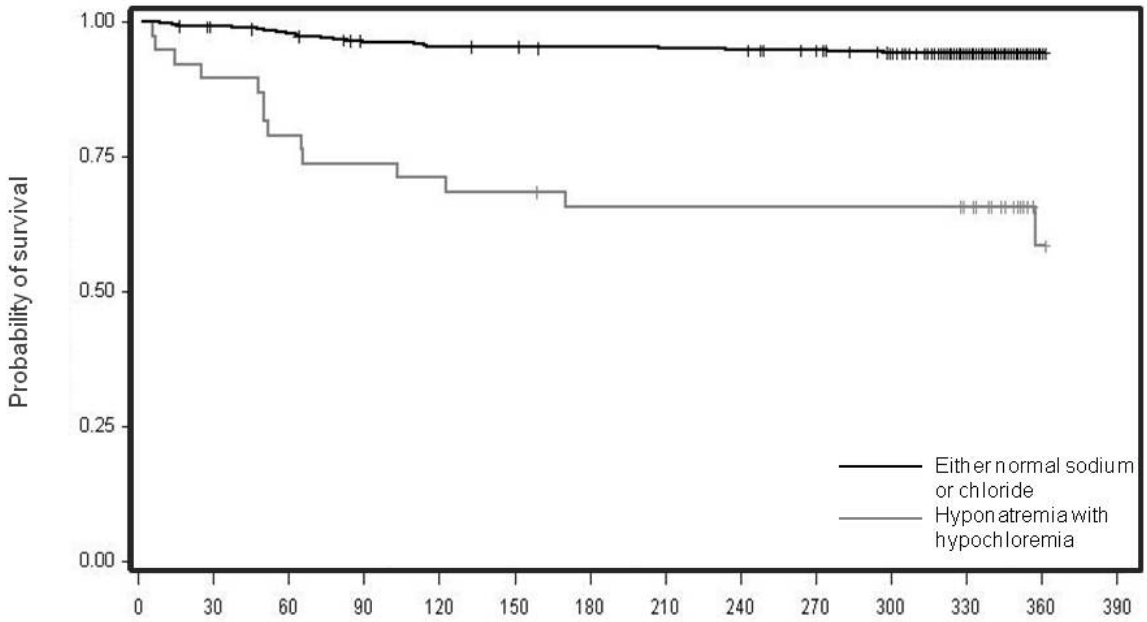
< 30	23 (10)	220 (90)	1.0	
≥ 30	30 (7)	388 (93)	3.7 (0.8-2.3)	
Body mass index (BMI), kg/m^2				
>18	18 (4)	481 (96)	1.0	1.0
<18	35 (22)	127 (78)	6.7 (3.8-11.8)	5.3 (2.6-10.6)
WHO clinical stage				
I/II/III	40 (7)	560 (93)	1.0	1.0
IV	13 (22)	48 (78)	3.3 (1.8-6.2)	1.5 (0.7-3.2)
Diagnosis of active tuberculosis				
No	46 (8)	559 (92)	1.0	
Yes	7 (13)	49 (87)	1.7 (0.7-3.7)	
CD4 cell count, cells/μL				
≥ 50	35 (7)	536 (93)	1.0	1.0
< 50	18 (20)	72 (80)	3.7 (2.1-6.5)	1.5 (0.7-3.2)
HIV plasma viral load, copies/mL				
< 100,000	17 (6)	289 (94)	1.0	
≥ 100,000	34 (10)	315 (90)	1.8 (1.0-3.2)	
Previous single-dose nevirapine exposure				
No	30 (8)	363 (92)	1.0	
Yes	23 (9)	245 (91)	1.1 (0.6-1.9)	
Hemoglobin, g/dL				
> 10	19 (5)	387 (95)	1.0	1.0
8-10	23 (12)	168 (88)	2.7 (1.5-4.9)	1.2 (0.6-2.4)
< 8	10 (21)	38 (79)	5.2 (2.4-11.2)	1.9 (0.8-4.8-)
White blood cells, cells/L				
> 2.5 $x10^9$	49 (9)	559 (91)	1.0	
≤ 2.5 $x10^9$	3 (8)	34 (92)	1.0 (0.3-3.3)	
Neutrophils, cells/L				
> 1.3 x 10^9	47 (9)	500 (91)	1.0	
≤ 1.3 x 10^9	4 (5)	74 (95)	0.5 (0.2-1.6)	
Platelets, cells/L				
≥ 125 x 10^3	45 (8)	555 (92)	1.0	
< 125 x 10^3	7 (16)	36 (87)	2.3 (1.0-5.1)	
Potassium, mmol/L				
> 3.4	43 (8)	515 (92)	1.0	
≤ 3.4	4 (9)	40 (91)	1.2 (0.4-3.5)	
Sodium, mmol/L				
> 135	18 (6)	282 (94)	1.0	
< 135 (hyponatremia)	29 (10)	275 (90)	1.7 (0.9-3.0)	
Chloride, mmol/L				

> 95	32 (6)	516 (94)	1.0	
≤ 95 (hypochloremia)	15 (27)	41 (73)	5.2 (2.8-9.7)	
Hyponatremia with hypochloremia				
No	33 (6)	533 (94)	1.0	1.0
Yes	14 (37)	24 (63)	7.8 (4.1-14.5)	4.5 (2.2-9.4)
Creatinine clearance, ml/min ‡				
>50	48 (8)	589 (92)	1.0	
≤50	5 (31)	11 (69)	3.9 (1.4-10.9)	
Baseline transaminases (AST/ALT)				
Grade = 0	38 (7)	512 (93)	1.0	
Grade ≥ 1 §	15 (14)	96 (86)	2.0 (1.1-3.7)	
Albumin, g/L				
> 34	15 (4)	353 (96)	1.0	1.0
< 34	33 (13)	222 (87)	3.4 (1.8-6.2)	1.8 (0.9-3.6)

Data presented are no. (%).
* Women not known to have died included 576 women who were alive and continuing care after one year of ART and 32 women lost to follow-up or who withdrew from the study.
† The final multiple Cox proportional hazard model included 586 (89%) of 661 women with complete data (no missing data) for the following variables: country, BMI, CD4 cell count, WHO stage, hemoglobin, sodium and chloride, and albumin. Compared with women with complete data, women who were missing baseline data (n=75) were all Zambian and were less likely to have WHO clinical stage 4 disease (p=0.03) but did not differ by baseline CD4 cell count, baseline BMI, or probability of death.
‡ Calculated using the Cockcroft Gault equation
§ Grade 1 = 1.25 upper limit of normal

Figure Legend

Figure 1: Kaplan-Meier estimates of the probability of survival during the first year of antiretroviral therapy stratified by baseline serum sodium and chloride values among HIV-infected Zambian and Kenyan women (N = 661), 2005-2007.



Number of patients at risk					
Either normal sodium or chloride	623	537	528	521	422
Hyponatremia with hypochloremia	38	28	24	24	21