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Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia

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Abstract

Objective—To examine the association between baseline renal insufficiency and mortality among adults initiating antiretroviral therapy (ART) in urban African setting.

Design—Open cohort evaluation

Methods—We examined mortality according to baseline renal function among adults initiating ART in Lusaka, Zambia. Renal function was assessed by the Cockcroft-Gault method, the Modification of Diet in Renal Disease (MDRD) equation, and serum creatinine.

Results—From April 2004 to September 2007, 25,779 individuals started ART with an available creatinine measurement at baseline. When creatinine clearance was calculated by the Cockcroft-Gault method, 8,456 (33.5%) had renal insufficiency: 73.5% were mild (60-89 mL/min), 23.4% moderate (30-59 mL/min), and 3.1% severe (<30 mL/min). Risk for mortality at or before 90 days was elevated for those with mildly (adjusted hazard ratio [AHR]=1.7; 95%CI=1.5-1.9), moderately (AHR=2.3; 95%CI=2.0-2.7), and severely (AHR=4.1; 95%CI=3.1-5.5) reduced creatinine clearance. Mild (AHR=1.4; 95%CI=1.2-1.6), moderate (AHR=1.9; 95%CI=1.5-2.3), and severe (AHR=3.6; 95%CI=2.4-5.5) insufficiency were also associated with increased mortality after 90 days, when compared to those with normal renal function. Trends were similar when renal function was estimated with MDRD or serum creatinine.

Conclusions—Renal insufficiency at time of ART initiation was prevalent and associated with increased mortality risk among adults in this population. These results have particular relevance for settings like Zambia, where tenofovir - a drug with known nephrotoxicity - has been adopted as part of first-line therapy. This emphasizes the need for resource-appropriate screening algorithms for renal disease, both as part of ART eligibility and pre-treatment assessment.

Keywords

HIV; renal disease; mortality; survival; antiretroviral therapy; sub-Saharan Africa; Zambia

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Introduction

Chronic infection with HIV is associated with numerous renal complications, both direct (e.g., HIV-associated nephropathy) and indirect (e.g. opportunistic infections, medications) in etiology [1-6]. Regardless of the underlying cause, however, renal insufficiency has been shown to be a significant, independent risk factor for mortality among HIV-infected patients. Two large cohorts in the United States - the HIV Epidemiology Research Study (HERS) and the Women's Interagency HIV Study (WIHS) - demonstrated a 2 to 2.5-fold risk of death among HIV-infected women with serum creatinine ≥ 1.4 mg/dL (equivalent to 123.8 μmol/L) [7,8]. Similar findings have been observed in hospital settings in both the industrialized and developing world [9,10]. Despite high burdens of both HIV and renal disease in sub-Saharan Africa [11,12], few studies to date have investigated whether these disease processes may have a combined effect on patient outcomes. In this analysis, we examined the association between baseline renal function and mortality among adults initiating antiretroviral therapy (ART) in a large public sector HIV care and treatment program in Lusaka, Zambia.

Methods

Analysis cohort

We analyzed data from a cohort of HIV-infected, ART-naïve adults initiating treatment across 18 primary care facilities within the Lusaka, Zambia public health sector. Protocols for patient care at these sites follow WHO guidelines and have been described elsewhere [13,14]. Briefly, patients documented HIV-positive sero-status undergo history and physical exam (including WHO clinical staging for HIV) and blood is collected for $CD4^+$ cell count. Those with $CD4^+$ < 200 cells/μL, WHO stage 4, or WHO stage 3 and CD4 count < 350 cells/μl are eligible for ART-based treatment. Local guidelines do not explicitly include measure of renal dysfunction (e.g. elevated serum creatinine, proteinuria) as indications for initiating ART [15]. Prior to initiating ART, screening tests for hematologic, renal, and hepatic function are performed. If serum creatinine is found to be equal to or greater than 120 μmol/L, creatinine clearance is calculated via the Cockcroft-Gault equation. Antiretroviral drug dosages are then adjusted accordingly.

For this analysis, we used estimates of creatinine clearance via the Cockcroft-Gault formula as our primary measure of renal function [16]. This surrogate measure of glomerular filtration rate (GFR) has been validated in sub-Saharan Africa [17] and is commonly used in the region to describe renal outcomes for clinical practice and research [18-20]. We used published clinical guidelines from the U.S. National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) to categorize renal insufficiency [21]. Creatinine clearance of ≥ 90 mL/min was considered normal. Individuals with a creatinine clearance of 60 - 89 mL/min (K/DOQI stage 2) were categorized as mild renal insufficiency; 30 - 59 mL/min as moderate insufficiency (K/DOQI stage 3); and < 30 mL/min as severe insufficiency (K/DOQI stage 4 and 5).

We performed two secondary analyses using other measures of renal function: serum creatinine levels alone and GFR calculated by the Modification of Diet in Renal Disease (MDRD) equation [22]. Because threshold values for serum creatinine are not well-defined in the medical literature [23], we relied upon commonly used cut-points from our clinical practice. A creatinine value was considered normal if ≤ 120 μmol/L. Renal insufficiency was considered mild if creatinine was 121 - 150 μmol/L; moderate if creatinine was 151 - 200 μmol/L; and severe if creatinine was > 200 μmol/L. The aforementioned K/DOQI-based categories for renal insufficiency were used for MDRD estimates of GFR.

We included adult patients (> 15 years of age) who were treatment-naïve, had a baseline creatinine result, and initiated ART between May 1, 2004 and September 30, 2007 (when the analysis dataset was frozen). The primary outcome of this analysis was mortality. Deaths were ascertained by reports from clinical facilities, home-based care organizations and follow-up visits by community workers. When the exact date of death was uncertain, we assumed it to be midpoint between the last kept appointment and the date of the report. Individuals who had withdrawn from the program were censored as of the date of their withdrawal. Those who were lost to follow up (defined as at least 30 days late for a clinical or pharmacy appointment) were censored as of October 1, 2007 or 30 days after the last scheduled appointment, whichever came first.

Statistical methodology

We calculated the prevalence of baseline renal insufficiency with 95% confidence intervals. Medical and demographic characteristics were compared using Student's t-test or Chi-square statistics. Crude mortality rates were compared via the z-test. All p-values were two-sided. We further calculated multivariable associations using adjusted relative risk (ARR) with 95% confidence intervals via modified Poisson regression and robust error variances [24,25]. We evaluated the association of renal insufficiency with mortality over time using Kaplan-Meier curves, stratified by disease severity. Log-rank tests were used to identify statistical differences between the groups.

In previous analyses, hazard for death was found to be markedly higher in the first 90 days of ART when compared to after 90 days [13]. For this reason, we used Cox proportional hazards regression to estimate the hazard ratios for mortality across over two separate periods: before or at 90 days and after 90 days. We successfully tested the proportional hazards assumption for both models, using the Kolmogorov-type supremum test [26]. Crude analyses were followed by multivariable analyses adjusting for factors known to be associated with mortality in this population: baseline $CD4^+$ cell count, WHO stage, and hemoglobin [13].

Similar analyses were performed using our secondary measures of renal function, serum creatinine and MDRD-estimated GFR. In addition to the aforementioned factors, age, sex and body mass index (BMI) were added to the serum creatinine model; BMI was added to the MDRD model. All analyses were performed with SAS version 9.1.3 (SAS Institute; Cary, North Carolina). Use of these routine clinical data was approved by the Institutional Review Boards of the University of Zambia, the U.S. Centers for Disease Control and Prevention, and the University of Alabama at Birmingham.

Results

From May 1, 2004 to September 30, 2007, 36,289 treatment naïve adults enrolled in the Lusaka district program and initiated ART. Baseline serum creatinine was documented in 25,779 (71.0%) of these individuals. 10,510 (29.0%) individuals did not have a creatinine result recorded and were thus excluded from the analysis. When we compared individuals with reported baseline serum creatinine results to those without, we found the populations did not differ according to WHO stage, baseline hemoglobin, or baseline BMI (data not shown). Those with a documented serum creatinine, however, were slightly more likely to be male (39.6% vs. 37.7%, $p < 0.001$) and had slightly higher baseline $CD4^+$ cell counts (148 vs. 141 cells / uL, $p < 0.001$). Although some of these discrepancies reached statistical significance, none are believed to be meaningful clinically. Crude mortality rate did not differ between those with baseline serum creatinine (8.4 per 100 person-years, 95% confidence interval [CI] = 8.1 - 8.8) and those without this data (8.0 per 100 person-years, 95%CI = 7.6 - 8.4; $p = 0.11$). The full cohort profile is shown as Figure 1.

Among the 25,779 individuals with baseline serum creatinine, 25,249 (97.9%) had complete individual data (e.g. weight, age, sex) for calculation of creatinine clearance using the Cockcroft-Gault formula. We found 8,456 (33.5%; 95% CI: 32.9%, 34.1%) had renal insufficiency. Of these, 6,216 (73.5%) of them were mild, 1,976 (23.4%) were moderate, and 264 (3.1%) were severe. When compared to those with normal creatinine clearance, several covariates were associated with renal disease (Table 1). In multivariable analysis, these predictors included female sex (ARR = 1.2; 95% CI: 1.1, 1.2), increasing age (ARR = 1.5 per 10 years; 95% CI: 1.4, 1.5), hemoglobin < 8 g / dL (ARR = 1.5; 95% CI: 1.4, 1.6), BMI < 16 kg/m^2 (ARR = 1.7; 95% CI: 1.6, 1.8), and WHO stage 3 (ARR = 1.2; 95% CI: 1.2, 1.3) or stage 4 (ARR = 1.3; 95% CI: 1.2, 1.4). Risk for renal insufficiency increased slightly as $CD4^+$ cell counts decreased. When compared to individuals with $CD4^+$ cell counts over 200 cells/μL, those with $CD4^+$ counts between 50 - 199 cells/μL (ARR = 1.2, 95% CI: 1.1, 1.2) and those with $CD4^+$ counts less than 50 cells/μL (ARR = 1.4, 95% CI: 1.4, 1.5) were more likely to have reduced creatinine clearance at time of enrollment.

In Kaplan-Meier analysis, two-year survival was highest among those with normal creatinine clearance (91.1%), followed by mild (85.8%), moderate (78.8%), and severe (61.2%) renal insufficiency (log rank $p < 0.001$; Figure 2). In a Cox proportional hazards model adjusting for potential confounders, risk for mortality ≤ 90 days was elevated for those with mildly (adjusted hazard ratio [AHR] = 1.7; 95% CI: 1.5, 1.9), moderately (AHR = 2.3; 95% CI: 2.0, 2.7), and severely (AHR = 4.3; 95% CI: 3.1, 5.5) reduced creatinine clearance. When compared to individuals with normal renal function, similar observations were noted in post-90 day mortality: mild insufficiency (AHR = 1.4; 95% CI: 1.2, 1.6), moderate insufficiency (AHR = 1.9; 95% CI: 1.5, 2.3), and severe insufficiency (AHR = 3.6; 95% CI: 2.4, 5.5; Table 2).

We performed secondary analysis using other estimates of renal insufficiency. Baseline serum creatinine was elevated in 979 of 25,779 individuals in our analysis population (3.8%, 95% CI: 3.7%, 4.0%). Of these, half had mild renal insufficiency (n = 503, 51.4%); the remainder had moderate (n = 242, 24.7%) or severe (n = 234, 23.9%) disease. When GFR was calculated by the MDRD equation, 3,209 individuals (12.4%; 95% CI: 12.0%, 12.9%) had renal insufficiency: 2,397 (74.7%) of them were mild, 642 (20.0%) were moderate, and 170 (5.3%) were severe. Regardless of measure of renal function in these secondary analyses, similar survival trends were observed according to renal insufficiency categories in Kaplan-Meier analysis (Figure 2). When mortality risk was assessed using a Cox proportional hazards model, risk for mortality gradually increased as renal insufficiency worsened, both ≤ 90 days and > 90 days (Table 2).

Discussion

In this programmatic cohort, we found a high baseline prevalence of renal insufficiency among individuals intiating ART. One-third demonstrated some degree of renal impairment when the Cockcroft-Gault method was used. This finding is concerning, since renal insufficiency - at all grades - was associated with increased risk for death. Even individuals with mild insufficiency had nearly a two-fold increase in early mortality when compared to those with no renal dysfunction. Like factors such as body mass index and hemoglobin [13,27-29], baseline renal function appears to be an important independent predictor of survival among HIV-infected individuals initiating ART in Africa.

Although these observational data do not establish a direct causal relationship between renal insufficiency and mortality, they do indicate the urgent need for further study of criteria for starting ART. In the mean time, it would seem reasonable to consider renal function screening - by serum creatinine measurement - for all HIV-infected patients where feasible. Measurement with urine protein should also be considered, since it may help to differentiate HIV-associated

nephropathy (HIVAN) from other etiologies. Early and on-going assessment for renal insufficiency among individuals who do not immediately qualify for ART may also be an important strategy, given the rapid and severe clinical course associated with HIVAN [30]. In cases where a diagnosis of HIVAN is made via biopsy - or highly suspected based on non-biopsy algorithms [31] - a trial of empiric ART could preserve long-term renal function and improve clinical outcomes.

In settings where renal insufficiency is diagnosed but the etiology is unknown, provision of ART in itself has been shown to improve renal function [18]. However, there may also be a role for adjunctive interventions. Small studies have demonstrated improved outcomes with use of corticosteroids [32,33] and ACE inhibitors [34,35] among patients with HIVAN. Empiric treatment with these interventions may be reasonable when a patient's initial response to ART is marginal or when clinical expertise and laboratory systems allow for the close patient monitoring. These measures could be particularly important in resource-limited settings like Zambia, where there is only one hemodialysis center available to support patients with either acute or chronic renal failure.

We observed a high prevalence of renal insufficiency among individuals initiating ART when the Cockcroft-Gault method was used. Our findings have particular relevance for HIV treatment locally, since the Zambian Ministry of Health recently introduced the nucleotide reverse transcriptase inhibitor tenofovir as part of first-line therapy. Although tenofovir has demonstrated efficacy, low pill burden, and a favorable safety profile [36], dose adjustments are needed to prevent chronic renal failure when creatinine clearance drops below 50 mL / min [37-39]. In our analysis, approximately 5% of patients would have required tenofovir dose adjustments if the drug had been used at the time of ART initiation. Nearly 30% would have benefited from serial creatinine monitoring following initiation of tenofovir-based ART due to mild to moderate baseline impairment (i.e. creatinine clearance of 50 - 89 mL / min). These considerations should probably be included in future cost-benefit analyses of tenofovir use in resource limited settings. While a strategy of routine screening will increase costs in resource-constrained settings, this must be balanced against the risk of iatrogenic renal failure. Similar concerns should be raised for other routinely used drugs with known renal toxicities, including antiretroviral (e.g. indinavir) or antimicrobial (e.g. aminoglycocides, trimethoprim-sulfamethoxazole) agents.

The prevalence of renal insufficiency varied significantly when measures other than Cockcroft-Gault-derived creatinine clearance were evaluated. Only 4% met criteria when serum creatinine was used alone; 12% met criteria when GFR was calculated via the MDRD formula. Both of these measures will likely require further validation in African settings, where malnutrition and lowered muscle mass might lead to lower measurements overall. Establishment of regionally appropriate screening cut-offs for renal insufficiency - particularly for serum creatinine [23] - could be useful in settings like Lusaka, where the majority of HIV care is provided by non-physician clinicians [13,14].

One limitation of this analysis was the high proportion of individuals with missing serum creatinine results: nearly 30% of patients initiating ART did not have a recorded baseline value. The reasons for this are varied, but mostly relate to the rapid nature of service scale-up in already busy primary care clinics (e.g. patient refusals, insufficient samples, lost laboratory results, oversight by health provider). Since the populations with and without serum creatinine appeared comparable according to important demographic characteristics and mortality risk factors, we believe the effect of ascertainment bias is likely small. Another limitation was the lack of detailed information regarding the possible etiology of renal insufficiency. Due to prohibitive cost and limited availability, access to histological diagnoses through renal biopsy is out of reach for most individuals seeking care in the Lusaka public sector. Routine urinalysis

is not standard practice at most sites; information regarding acute and chronic medical co-morbidities is not routinely collected. Lastly, information describing renal function over time could have provided greater insight into the relationship between baseline renal insufficiency and death; however, these data are not reliably collected in our setting. The impact of ART on long-term renal outcomes is another area requiring further study, particularly in settings where screening modalities may be limited.

In summary, we observed higher risk for mortality among patients with renal insufficiency at time of ART initiation, even among individuals with mild renal disease. This finding was consistent across different measures of renal function and independent of other known predictors of mortality. Our results suggest that, where feasible, screening for renal function should be instituted as part of ART expansion programs, particularly when drugs with known nephrotoxicities have been incorporated into HIV treatment. Algorithms for more aggressive assessment and management of renal insufficiency should also be developed specifically for settings with limited diagnostic capabilities.

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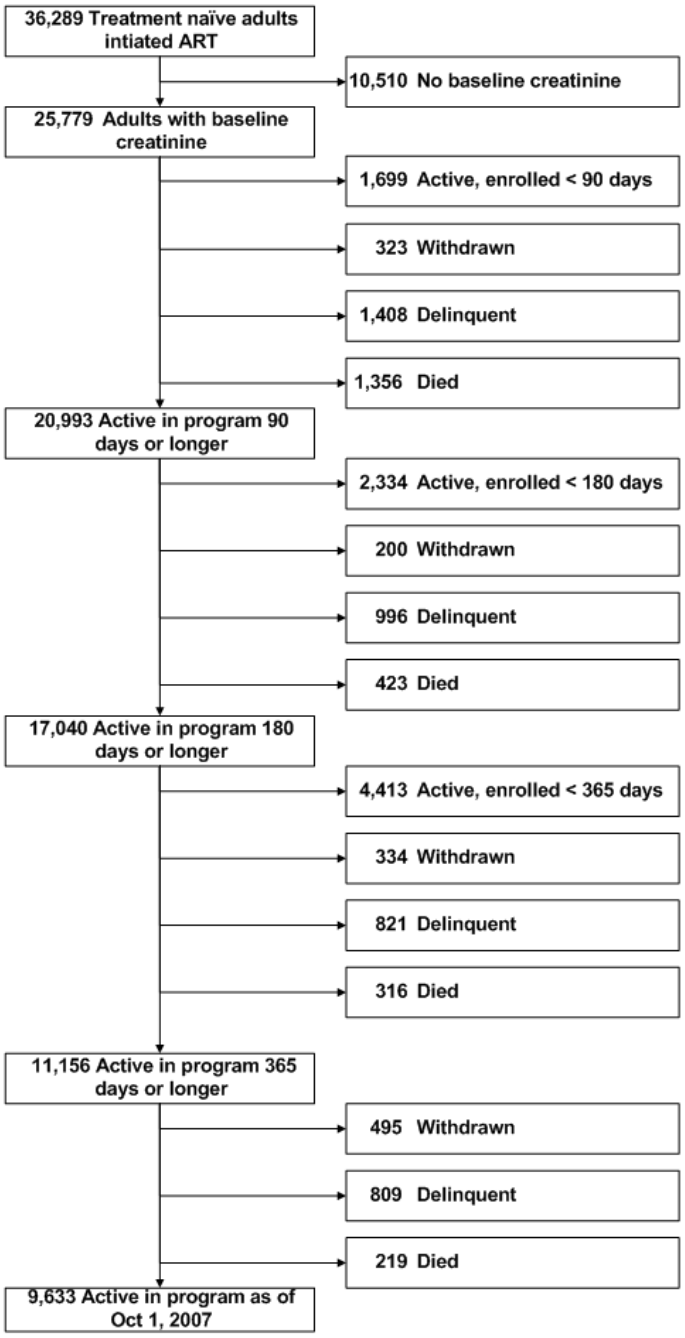
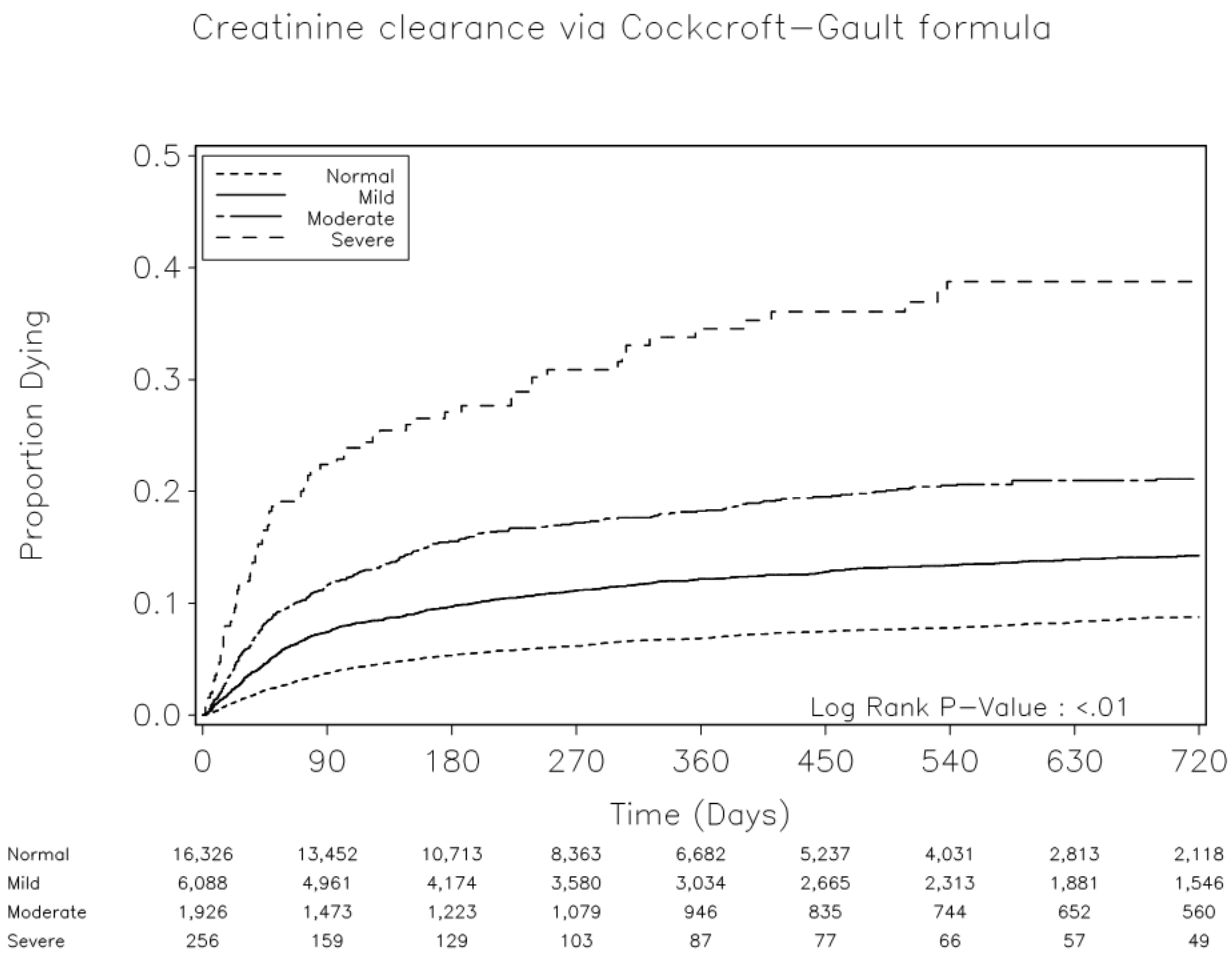
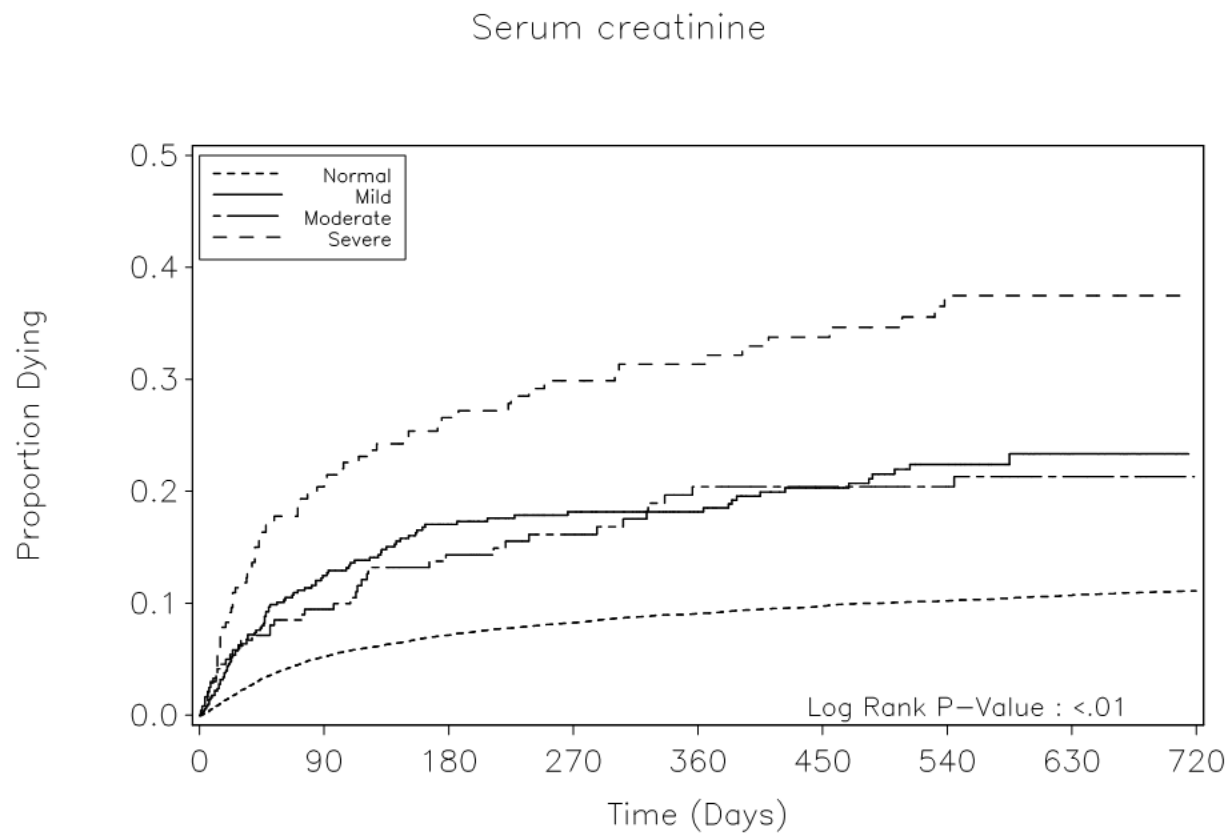


Figure 1.



Normal	16,326	13,452	10,713	8,363	6,682	5,237	4,031	2,813	2,118
Mild	6,088	4,961	4,174	3,580	3,034	2,665	2,313	1,881	1,546
Moderate	1,926	1,473	1,223	1,079	946	835	744	652	560
Severe	256	159	129	103	87	77	66	57	49



Normal	24,800	20,269	16,454	13,298	10,893	8,907	7,207	5,438	4,291
Mild	503	393	315	272	239	205	177	150	128
Moderate	242	183	148	129	108	100	90	78	70
Severe	234	148	123	101	87	76	64	58	48

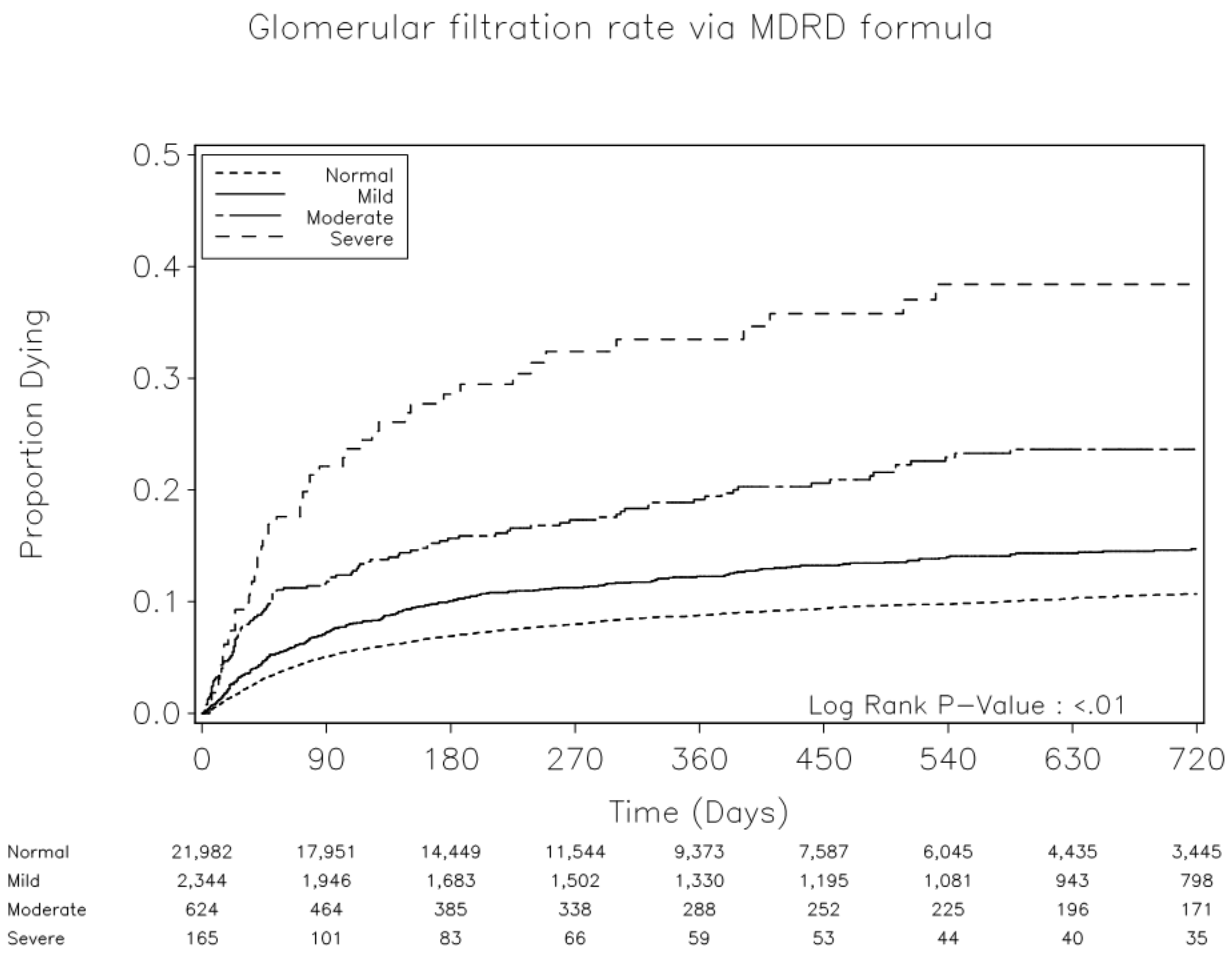


Figure 2.

Table 1

Comparison of patients with and without decreased creatinine clearance at time of ART initiation according to Cockcroft-Gault formula, Lusaka, Zambia (May 2004 - September 2007)

	Normal creatinine clearance (>90 mL / min)		Decreased creatinine clearance (≤ 90 mL / min)		
	N	Value	N	Value	p value
Age, mean (SD)	16,793	33.7 (7.9)	8,456	38.5 (9.9)	<.001[+]
Female	10,150	60.4%	5,083	60.1%	0.60[*]
Body Mass Index					
Female, mean kg/m^2 (SD)	9,486	21.3 (4.1)	4,379	19.1 (3.4)	<.001[+]
Male, mean kg/m^2 (SD)	6,222	19.9 (3.1)	2,978	18.6 (3.1)	<.001[+]
CD4+ count, mean cells/μL(SD)	16,326	157 (114)	8,270	132 (106)	<.001[+]
CD4+ count < 50 cells/μL	2,438	14.9%	1,956	23.7%	<.001[*]
Hemoglobin, mean g/dL	15,773	11.0 (2.1)	8,016	10.3 (2.2)	<.001[+]
Hemoglobin < 8 g/dL	1,094	6.9%	1,139	14.2%	<.001[*]
WHO Stage					
I	1,995	11.9%	608	7.2%	<.001[*]
II	3,622	21.7%	1,441	17.1%	
III	9,566	57.3%	5,378	63.9%	
IV	1,516	9.1%	993	11.8%	
Regimen					
Zidvoudine + lamivudine + nevirapine	8,356	49.8%	3,726	44.1%	<.001[*]
Zidvoudine + lamivudine + efavirenz	742	4.4%	286	3.4%	
Stavudine + lamivudine + nevirapine	6,601	39.3%	3,757	44.4%	
Stavudine + lamivudine + efavirenz	1,036	6.2%	633	7.5%	
Other	58	0.3%	54	0.6%	

[*]Chi-square 530 patients are missing a baseline weight and were excluded from this table as the Cockcroft-Gault creatinine clearance could not be calculated

[+]Student's t-test 530 patients are missing a baseline weight and were excluded from this table as the Cockcroft-Gault creatinine clearance could not be calculated

Table 2

Mortality among patients starting antiretroviral therapy according to three measures of renal function, Lusaka, Zambia (May 2004 - September 2007)

	Creatinine clearance via Cockcroft-Gault calculation		Serum creatinine		Glomerular filtration rate via MDRD calculation	
	(mL/min)		(μmol/L)		(mL/min per 1.73 m^2)	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Mortality before or at 90 days						
Normal renal function	Ref	Ref	Ref	Ref	Ref	Ref
Renal Insufficiency						
Mild	2.0 (1.8 - 2.3)	1.7 (1.5 - 1.9)	2.5 (1.9 - 3.2)	1.7 (1.3 - 2.3)	1.5 (1.2 - 1.7)	1.3 (1.1 - 1.6)
Moderate	3.3 (2.8 - 3.8)	2.3 (2.0 - 2.7)	1.9 (1.3 - 2.9)	1.3 (0.8 - 2.2)	2.5 (2.0 - 3.2)	1.7 (1.3 - 2.3)
Severe	7.0 (5.4 - 9.2)	4.1 (3.1 - 5.5)	4.5 (3.4 - 6.1)	2.6 (1.8 - 3.8)	5.2 (3.7 - 7.2)	3.0 (2.0 - 4.6)
Mortality after 90 days						
Normal renal function	Ref	Ref	Ref	Ref	Ref	Ref
Renal Insufficiency						
Mild	1.5 (1.3 - 1.7)	1.4 (1.2 - 1.6)	2.0 (1.5 - 2.8)	1.5 (1.0 - 2.3)	1.4 (1.1 - 1.7)	1.3 (1.1 - 1.7)
Moderate	2.3 (1.9 - 2.7)	1.9 (1.5 - 2.3)	2.4 (1.6 - 3.7)	1.8 (1.1 - 3.2)	2.4 (1.8 - 3.2)	1.9 (1.3 - 2.7)
Severe	4.5 (3.0 - 6.6)	3.6 (2.4 - 5.5)	3.6 (2.4 - 5.4)	3.0 (1.8 - 5.0)	4.1 (2.6 - 6.5)	3.8 (2.2 - 6.5)

*All models adjusted for baseline CD4 count, WHO stage, hemoglobin, and initial antiretroviral regimen. Body mass index was included in the models for serum creatinine and MDRD creatinine clearance. Age and sex were included in the model for serum creatinine only