

The Relationships between Renal Dysfunction and Clinical Outcomes in HIV-Infected Kenyans Not Requiring Immediate ART

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ABSTRACT

Background: Renal dysfunction is associated with worse clinical outcomes in ART-naïve, HIV-infected U.S. women. The objective of this analysis is to determine if renal dysfunction in patients (both men and women) not meeting criteria for ART initiation at enrollment on an HIV care program in western Kenya is associated with HIV disease progression and early mortality.

Methods: The electronic medical records of all adult, non-pregnant patients with WHO stage 1 or 2 disease and with CD4 cell count <200mm³ who enrolled in USAID-AMPATH Partnership between February 2002 and October 2007 were retrospectively reviewed. The association between renal function (CrCl estimated by Cockcroft-Gault; GFR estimated by simplified MDRD) at enrollment and time to CD4 cell count decline to <200mm³, development of WHO stage 3 or 4 disease, mortality, and loss to follow-up were determined. Hazard ratios (HR [95% CI] per 1 unit) were estimated using Cox regression models.

Results: 8737 HIV-infected Kenyans (27% men, 68% WHO stage 1) met study eligibility. Median (IQR) enrollment CD4 cell count, age, and hemoglobin were 386 (282, 546)/mm³, 35 (29, 43) years, and 12.6 (10.9, 14.0) g/dL, respectively. Median (IQR) follow-up was 53 (25, 91) weeks. At enrollment, 36%, 45%, and 19% had CrCl <89, 60-89, and <60mL/min, respectively; 58%, 33%, and 9% had GFR <89, 60-89, and <60mL/min/1.73m², respectively. At enrollment, higher CrCl was significantly associated with WHO stage 1 disease (vs. stage 2), higher CD4 cell count, and higher hemoglobin (all P<0.0001). After adjustment for enrollment age, sex, CD4 cell count, and hemoglobin, higher enrollment CrCl was associated (all P<0.0001) with slower decline in CD4 cell count to <200mm³ [0.997 (0.994, 1.000)], slower development of WHO stage 3 or 4 [0.992 (0.989, 0.995)], and with longer time to loss to follow-up [0.997 (0.995, 0.999)]; there was no association with mortality. Similar associations were seen between higher GFR and slower development to WHO stage 3 or 4 and longer time to loss to follow-up, but GFR was not associated with time to CD4 <200mm³ or mortality.

Conclusion: Renal function is an independent predictor of HIV disease progression in Kenyans not requiring ART at presentation and, as such, may provide additional utility in identifying those who may benefit more from earlier initiation of ART. The cost of measuring serum creatinine at program enrollment may be justified in this context.

BACKGROUND

- With the rollout of ART increasing in resource-limited settings, it may be possible to provide treatment to asymptomatic patients with higher CD4 cell counts.
- Identifying such patients is difficult without performing more expensive tests such as HIV viral loads.
- Renal dysfunction has been associated with faster times to new AIDS-defining illness and mortality in HIV-infected women in the U.S.
- We investigated the role of renal dysfunction, which is more easily and cheaply measured than viral loads, in predicting HIV disease progression in Kenya.

METHODS

- We performed a retrospective analysis of all USAID-AMPATH Partnership care program enrollees from 2002-2007; adults with CD4 above 200cells/μL and with WHO stage 1 or 2 disease were included.
- Those who had previously received ART, who required ART at enrollment, who were pregnant at enrollment, or who became pregnant during the course of follow-up were excluded.
- Renal function estimated as creatinine clearance (CrCl, using Cockcroft-Gault) and as glomerular filtration rate (GFR, using simplified MDRD).
- Hazard ratios based on the degree of renal dysfunction at enrollment were estimated using Cox regression models for the following endpoints: CD4 <200cells/μL, WHO stage 3 or 4 disease, mortality, loss to follow-up.
- Models adjusted for enrollment age, sex, CD4, WHO stage, hemoglobin, and subsequent ART initiation.

ENROLLMENT CHARACTERISTICS

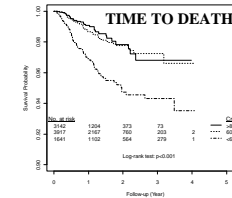
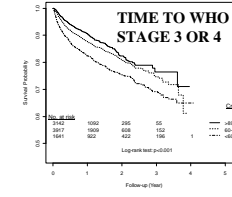
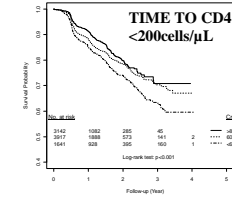
- N=8737; Median (IQR) follow-up was 1 (0.5, 2.0) year.
- Median (IQR) CD4 cell count, age, and hemoglobin were 386 (282, 546)/μL, 35 (29, 43) years, and 12.6 (10.9, 14.0) g/dL, respectively.
- 36%, 45%, and 19% had CrCl >89, 60-89, and <60mL/min, respectively; 58%, 33%, and 9% had GFR >89, 60-89, and <60mL/min/1.73m²

RESULTS*

Outcome	Enrollment Variable	HR (95% CI)**
Time to CD4 <200cells/μL	CrCl 60-89 mL/min	1.078 (0.920, 1.262)
	CrCl < 60 mL/min	1.227 (1.027, 1.467)
	GFR 60-89 mL/min/1.73 ²	1.052 (0.918, 1.205)
Time to WHO stage 3 or 4	GFR < 60 mL/min/1.73 ²	1.201 (0.997, 1.447)
	CrCl 60-89 mL/min	1.194 (1.018, 1.399)
	CrCl < 60 mL/min	1.619 (1.351, 1.939)
Time to death	GFR 60-89 mL/min/1.73 ²	1.064 (0.926, 1.222)
	GFR < 60 mL/min/1.73 ²	1.427 (1.181, 1.724)
	CrCl 60-89 mL/min	1.023 (0.827, 1.267)
Time to lost to follow-up	CrCl < 60 mL/min	1.684 (1.005, 2.819)
	GFR 60-89 mL/min/1.73 ²	1.040 (0.711, 1.520)
	GFR < 60 mL/min/1.73 ²	0.962 (0.552, 1.676)
Time to death	CrCl 60-89 mL/min	1.095 (0.982, 1.221)
	CrCl < 60 mL/min	1.264 (1.105, 1.445)
	GFR 60-89 mL/min/1.73 ²	1.112 (1.004, 1.232)
Time to death	GFR < 60 mL/min/1.73 ²	1.262 (1.086, 1.467)

*See Abstract for models using CrCl or GFR as continuous predictors

**Reference is CrCl >89mL/min or GFR >89mL/min/1.73²



DISCUSSION

- Renal dysfunction was common in this antiretroviral-naïve Kenyan population with CD4 cell counts above 200/μL and with WHO stage 1 or 2 disease.
- Estimates of renal function prevalence differed based on the use of CrCl or GFR, perhaps reflecting the incorporation of weight in the Cockcroft-Gault formula.
- Lower CrCl, but not lower GFR, was associated with shorter times to CD4 cell count decline to less than 200/μL and death.
- Both lower CrCl and GFR were associated with shorter times to WHO stage 3 or 4 disease and loss to follow-up.
- Renal dysfunction may be a surrogate marker of higher HIV-1 viral load or higher immune activation, neither of which was measured in this cohort.
- HIV-1-infected patients at greater need for earlier initiation of ART may be identified at first visit by measurement of serum creatinine and estimation of CrCl.
- Prospective studies evaluating the role of renal dysfunction as an easily obtained and inexpensive marker of HIV disease progression are needed to confirm these data.

ACKNOWLEDGEMENTS

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