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Baseline renal function predicts mortality in adolescents commenced on HIV antiretroviral therapy

As of 2018, over 1.5 million children were estimated to be living with HIV in sub-Saharan Africa [1]. Numerous studies have reported high rates of renal disease in this population but the impact of renal disease on clinical outcomes in children living with HIV from sub-Saharan Africa has yet to be described [2]. Data are similarly limited internationally. Further data are, therefore, needed to determine the impact of renal disease on long-term clinical outcomes.

We conducted a retrospective cohort study to investigate the prevalence of renal impairment and proteinuria, and to examine their relationship with mortality, amongst paediatric ART-naïve patients at the Newlands Clinic, a nongovernmental organization funded by charitable donors in Harare, Zimbabwe. Ethical approval for this study was granted by the Medical Research Council of Zimbabwe (MRCZ/E/258) and all research activities were conducted in accordance with the Declaration of Helsinki.

Data were extracted from clinic visits between January 2010 and January 2019. Patients were eligible for inclusion if they were between the ages of 12 and 17 years old, ART-naïve, and had baseline (prior to the initiation of ART) $CD4^+$ count and serum creatinine measurements and at least one $CD4^+$ count and one creatinine measurement after commencement of ART. Potential predictors of mortality included sex, age, baseline $CD4^+$ count less than 200 cells/μl, baseline renal impairment and proteinuria (≥1+ on urine dipstick), and were assessed by logistic regression. Predictors with a P less than 0.1 in univariate analysis were included in a multivariate model. Preexisting renal impairment was defined as a baseline estimated glomerular filtration rate (eGFR) less than 90 ml/min/1.73 m^2, calculated using the Full Age Spectrum formula [3]. For all analyses, $P = 0.05$ was considered statistically significant.

Between January 2010 and January 2019, 284 adolescent patients with HIV infection were commenced on ART at the Newlands Clinic. Two patients were excluded from the study, as they had no follow-up creatinine measurement. A total of 282 patients were thus included in the analysis, with a median follow-up time of 4.7 years (IQR = 2.2–7.5).

Sex distribution was approximately equal (55% girls) and median baseline age was 14.3 years (IQR = 14.1–14.5), with the range of ages extending from 12 to 17 years. Thirteen percent of patients had preexisting renal impairment (baseline eGFR ≤90 ml/min/1.73 m^2). Forty-three percent of patients had a $CD4^+$ count 200 cells/μl or less. Data on urinary protein were available for 209 patients (72%), of which 7% had proteinuria at baseline. Preexisting renal impairment was more common in male than female individuals (21% vs. 6%, $P < 0.001$), but there were no differences in age ($P = 0.489$), proteinuria ($P = 0.861$) or $CD4^+$ count ($P = 0.693$). Twenty-five deaths were recorded over the study period, representing 9% of the cohort. Potential predictors of mortality were evaluated by logistic regression (Table 1).

Low baseline eGFR in HIV-infection was an independent predictor of mortality in our cohort. In other paediatric populations, HIV infection increased the risk of mortality among children with end-stage renal failure. One American study reported 2-year survival with focal

Table 1. Predictors of mortality in adolescents commenced on antiretroviral therapy.

	Univariate		Multivariate	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex (male)	1.97 (0.85–4.56)	0.112	–	–
Age (years)	0.92 (0.72–1.18)	0.507	–	–
Baseline eGFR <90 ml/min/1.73 m^2	2.30 (0.92–6.21)	0.099	3.05 (1.00–9.23)	0.050
Proteinuria	4.05 (1.16–14.17)	0.029	3.22 (0.86–12.09)	0.084
Baseline $CD4^+$ count <200 cells/μl	4.81 (1.86–12.46)	0.001	3.15 (1.06–9.23)	0.038

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

segmental glomerulosclerosis in the absence of HIV infection was 95% whereas survival was only 65% in those with HIV-associated nephropathy [4]. A similar disparity was reported in European children receiving renal replacement therapy [5].

Seven percent of patients in our study had proteinuria prior to initiation of ART, similar to the 3–8% reported in other paediatric studies from sub-Saharan Africa. This narrow range of estimates is somewhat surprising, given the variation in study populations, particularly with regards to antiretroviral use [6–9]. Two studies from Nigeria have reported substantially higher rates of proteinuria, approximately 3–4-fold greater than in our study [10,11]. The use of urinary protein-to-creatinine ratio to define proteinuria by Esezobor *et al.* [10] may account for some of this difference, as the use of albumin by other studies would have precluded detection of low-molecular-weight proteinuria [6–9]. Although proteinuria did not increase mortality risk in our study, this may have been a consequence of proteinuria data not being available for all patients.

The main limitation of this study were sample size considerations. The low number of deaths made it particularly sensitive to incomplete time of death information and precluded conventional time-to-event analysis. However, the use of a cohort analysis was unlikely to have created a particular bias in the assessment of predictors.

In conclusion, baseline renal impairment and severe immunodeficiency independently predicted mortality in a cohort of ART-naïve Zimbabwean adolescents living with HIV. The presence of these risk factors may be useful in identifying patients who would benefit from more intensive follow-up and management.

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Conflicts of interest

There are no conflicts of interest.

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Hepatitis B vaccination response and safety in people living with HIV/AIDS receiving HepB-CpG series

HepB-CpG (HEPLISAV-B; Dynavax, Emeryville, California, USA) is a two-dose hepatitis B virus (HBV) vaccination series approved for individuals over 18 years old [1,2]. HepB-CpG, administered at 0 and 1 month, contains a novel adjuvant that elicits a robust and specific innate immune response. This adjuvant differs from standard three-dose (20 μg at 0, 1, 6 months) recombinant series (Engerix-B; GlaxoSmithKline, Research Triangle Park, North Carolina, USA) containing an aluminum adjuvant causing a broader, nonspecific response.

Several phase 3, randomized, multicenter trials demonstrate that immunogenicity elicited by HepB-CpG is noninferior to standard three-dose HBV series in healthy and older adults including those with obesity, males, people with diabetes, and smokers [1,3–5]. 5–30% of immunocompetent individuals receiving standard series do not attain HBV seroprotection and nonresponse is higher among immunocompromised patients including people living with HIV/AIDS (PWH) [6–8]. A qualitative study reported an 86% (25/29) immune response rate to HepB-CpG among PWH of whom 68% were prior nonresponders to standard series [9]. Although HepB-CpG represents a simpler, highly immunogenic vaccination strategy, there is limited data in PWH.

We conducted a prospective longitudinal cohort study in our urban, Ryan-White funded clinic from October 2018 through May 2020. Patients who received two HepB-CpG vaccinations >1 month apart with the resulting hepatitis B surface antibodies (anti-HBs) collected >1 month after series completion were included in analysis. Individuals with an anti-HBs ≥10 IU/l were considered "responders" and an anti-HBs of <10 IU/l were "nonresponders." Electronic medical record (EMR) was used to assess for adverse safety events within 6 months and HIV viral load elevations, defined as an HIV viral load >200 copies/ml, within 3 months following either vaccination. Student's *t* tests for an unequal and equal variance were performed for age and CD4 count, respectively. Fisher exact test was used to compare additional baseline characteristics.

Eighty-seven patients received at least one dose of HepB-CpG with 65/87 (74.7%) meeting inclusion criteria. The response rate to HepB-CpG among PWH was over 86%. Cohort response and characteristics appear in Table 1. All nine nonresponders were historical nonresponders to ≥1 standard series. Nonresponders were significantly older with lower mean CD4 counts and a greater proportion of CD4 counts <350 cells/μl. One responder and one nonresponder had HIV viremia >200 copies/ml because

Table 1. Response and characteristics.

Response and characteristics	Total ($n = 65$)	Responders ($n = 56$)	Nonresponders ($n = 9$)	*P* value
Overall response		56/65 (86.2%)	9/65 (13.8%)	
Age (years), mean (range)		49.5 (22–77)	60.5 (49–69)	0.001
Sex [*n* (%)]				
Male	42/65 (64.6%)	37/56 (66.1%)	5/9 (55.6%)	0.709
Race [*n* (%)]				
African American	48/65 (73.9%)	42/56 (75.0%)	6/9 (66.7%)	0.687
Other	17/65 (26.1%)	14/56 (25.0%)	3/9 (33.3%)	
Prior HBV vaccine nonresponders		29/56 (51.8%)	9/9 (100%)	0.008
One prior complete HBV vaccine series		11/29 (37.9%)	6/9 (66.7%)	
Two prior complete HBV vaccine series		16/29 (55.2%)	3/9 (33.3%)	
One prior incomplete prior HBV vaccine series[a]		2/29 (6.9%)	0/9 (0.0%)	
CD4 (cells/μl) [*n* (%)], mean (range)		559.2 (59–2280)	349.4 (33–956)	0.089
CD4 < 350 (cells/μl)		14/56 (25.0%)	5/9 (55.6%)	0.109
HIV RNA < 200 copies/ml [*n* (%)]	$n = 45$[b]	36/38 (94.7%)	6/7 (85.7%)	0.406
BMI > 30 (kg/m^2)		25/56 (44.6%)	3/9 (33.3%)	0.721
Current tobacco use		20/56 (35.7%)	5/9 (55.6%)	0.289
Diabetes mellitus, type 2		15/56 (26.8%)	1/9 (11.1%)	0.433

[a]Two of three vaccines in HBV series received.
[b]Resulted viral load within 3 months of vaccine receipt.