Published in final edited form as:

J Acquir Immune Defic Syndr. 2016 January 1; 71(1): 65–69. doi:10.1097/QAI.0000000000000812.

Effects of tenofovir and amphotericin B deoxycholate co-administration on kidney function in patients treated for cryptococcal meningitis

Reuben Kiggundu, MBChB^{1,*}, Bozena M Morawski, MPH^{2,*}, Nathan C Bahr, MD², Joshua Rhein, MD^{1,2}, Abdu K Musubire, MMed¹, Darlisha A Williams, MPH^{1,2}, Mahsa Abassi, DO, MPH², Henry W Nabeta, MBChB¹, Kathy Huppler Hullsiek, PhD², David B Meya, MMed^{1,2,3}, and David R Boulware, MD, MPH² on behalf of the ASTRO-CM Team

¹Infectious Disease Institute, Makerere University, Kampala, Uganda ²University of Minnesota, Minneapolis, MN, USA ³School of Medicine, College of Health Sciences, Makerere University

Abstract

The effect of tenofovir and amphotericin co-administration on kidney function is poorly characterized. We measured creatinine during induction therapy and at 4-weeks post-diagnosis in Ugandans undergoing cryptococcal meningitis therapy, and classified as not receiving antiretroviral therapy (ART), receiving non-tenofovir ART, or receiving tenofovir-based ART. Longitudinal creatinine changes and Grade 2–4 creatinine adverse events were evaluated across groups. Creatinine concentrations were similar across ART groups. At 4 weeks post-diagnosis, creatinine was 0.25mg/dL higher than at diagnosis, but similar across groups. Adverse event incidence was also similar across ART groups. Tenofovir and amphotericin co-administration did not increase the risk of kidney dysfunction.

Keywords

cryptococcal meningitis; amphotericin B deoxycholate; tenofovir; renal toxicity

Introduction

Cryptococcal meningitis accounts for >30% of adult meningitis in sub-Saharan Africa.^{1–3} Amphotericin B deoxycholate (amphotericin), in combination with other antifungal medications, remains the mainstay of cryptococcosis treatment despite its toxicity.^{4–6} Amphotericin-related nephrotoxicity occurs from direct damage to renal tubules and constriction of the renal vasculature.⁷ Acute kidney injury has been estimated to occur in

Corresponding Author: Reuben Kiggundu, MBChB, Infectious Disease Institute, Makerere University, Mulago Hospital Complex, P.O. Box 22418 Kampala, Uganda, reubenkaaja@yahoo.com.

*These authors equally contributed to this manuscript

ASTRO-CM Team members: Lillian Tugume, Jonathan Dyal, Julie M Neborak, Alexa M King, Nathan Yueh, Jane Francis Ndyetukira, Cynthia Ahimbisibwe, Florence Kugonza, Alice Namudde, Alisat Sadiq, Tadeo Kiiza Kandole, Elissa K Butler, Julian Kaboggoza, Eva Laker, Andrew Akampura, Tony Luggya, Paul R Bohjanen, Andrew Kambugu.

Conflicts: There are no conflicts of interest.

30% of patients receiving amphotericin.⁷⁻¹⁰ Furthermore, concurrent administration of amphotericin with other non-tenofovir nephrotoxic agents, e.g. aminoglycosides, foscarnet, ganciclovir, has been shown to increase the risk of kidney toxicity.¹⁰⁻¹²

Given increasing access to antiretroviral therapy (ART) in sub-Saharan Africa and the relatively high prevalence of cryptococcal antigenemia,¹³ an increasing number of patients are receiving ART at the time of cryptococcal meningitis diagnosis. Whether amphotericin-related nephrotoxicity is exacerbated by ART is unknown. Tenofovir disoproxil fumarate (tenofovir) is of special concern, as tenofovir can induce kidney damage via proximal tubular cell dysfunction.¹⁴⁻¹⁸ Although tenofovir is part of first line ART worldwide,^{19,20} safety data guiding amphotericin and tenofovir co-administration are limited. The single *in vitro* and organ model study examining kidney interactions between amphotericin and tenofovir concluded that drug-drug interactions are unlikely at standard clinical doses of amphotericin and tenofovir.²¹ However, to guide clinical care, there is a need to characterize the effects of concurrent administration of amphotericin and tenofovir. We examined kidney function and the risk of kidney toxicity associated with amphotericin and tenofovir co-administration during cryptococcal meningitis therapy.

Materials and methods

From August 2013 through August 2014, 173 adults were enrolled in an open label pilot phase of the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis trial (ClinicalTrials.gov: NCT01802385) at Mulago Hospital in Kampala, Uganda. Inclusion criteria were: HIV infection, 18 years of age, positive cerebrospinal fluid (CSF) cryptococcal antigen, and written informed consent. Exclusion criteria included pregnancy, breastfeeding, jaundice, cirrhosis, and receipt of >2 days amphotericin at enrollment. The University of Minnesota and Ugandan institutional review boards approved the protocol.

All participants received high dose fluconazole (800-1200 mg/day), 7-14 days of amphotericin B deoxycholate (1.0 mg/kg/day, maximum 50 mg/day), 1.0L of intravenous saline before and 1.0L after amphotericin administration, trimethoprim-sulfamethoxazole prophylaxis, and universal electrolyte supplementation per World Health Organization guidelines.^{22,23} The duration of amphotericin-based induction therapy, while similar for most patients, was determined by the combination of 1) initial CSF fungal burden, 2) CSF fungal clearance, and 3) renal function (as evaluated by creatinine and potassium concentrations). Decisions to either administer <14 days amphotericin or to alternate days of amphotericin were made as clinically indicated by the above factors.

ART status was evaluated via participant/surrogate interview and chart review. At diagnosis, participants were classified as 1) not receiving ART (including ART-default 30 days prior), 2) receiving ART that did not currently include tenofovir, or 3) receiving ART that included tenofovir. In Uganda, tenofovir is only available as a fixed dose; barring adherence differences, all patients received similar doses of tenofovir and other components of their ART.

Serum creatinine was measured at diagnosis, and visit days 3, 7, 10, 14 and 28. Kidney function was estimated via 1) serum creatinine and 2) glomerular filtration rate. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (GFR_{CKD-EPI}) equation,²⁴ as it more accurately predicts mortality at higher glomerular filtration rates and in non-white populations, relative to the Modification of Diet in Renal Disease Study equation.²⁵ We evaluated adverse events related to kidney function via creatinine concentrations. Creatinine adverse events were classified per the National Institutes of Health, Division of AIDS (DAIDS) table for grading the severity of adverse events,²⁶ which defines creatinine adverse events as fold change from the upper limit of normal (ULN) by sex with Grade 2 as 1.4 – 1.8 times the ULN, Grade 3 as 1.9 – 3.4 times, Grade 4 as 3.5 times, and Grade 5 as creatinine-attributable mortality.

Statistical analysis

Kruskal-Wallis equality-of-populations and Fisher's exact tests were used to evaluate differences in creatinine and GFR_{CKD-EPI} across ART groups at diagnosis, the end of induction therapy (day 14), and 4 weeks post-diagnosis (day 28). Differences in serum creatinine and GFR_{CKD-EPI} (mL/min/1.73m²) across ART groups from baseline through 14, and from the end of induction therapy (14 days) through 28 days were evaluated using linear mixed models, with a random intercept for patient and a random slope for time. Similar linear mixed models evaluated differences in the rate of creatinine and GFR_{CKD-EPI} change over time across ART groups via an interaction term between time and ART group. Final multivariate models for serum creatinine and GFR_{CKD-EPI} included amphotericin B dose; and final multivariate models for creatinine also included sex. The effects of age, CD4+ T cells at diagnosis, systolic blood pressure at diagnosis, prior diagnosis of cryptococcal meningitis, and quantitative cryptococcal cultures were examined but not included in final linear mixed models.

All-cause mortality competing-risks regression evaluated differences in time-to-first Grade 2, 3, or 4 creatinine adverse event. Systolic blood pressure and dose of amphotericin were included in the time-to-event analysis. All statistical analyses were conducted in Stata/IC 13.1 (StataCorp, College Station, Texas), and evaluated against a Type I error rate of 0.05.

Results

Eight of 173 enrolled participants were excluded from analysis due to unknown ART status (n=4), no amphotericin receipt (n=3), or no creatinine measurement (n=1). Participant demographics and characteristics at diagnosis are similar to other cryptococcal meningitis cohorts,^{4,27} with the exception that ~45% of these patients were receiving ART at diagnosis. Of relevance to these analyses, participants receiving non-TDF-based ART have significantly elevated single-measure baseline systolic blood pressure (136 in patients receiving non-TDF-based ART versus 117 in patients receiving tenofovir-based ART or no ART).

Kidney function declined over the initial 2 weeks of hospitalization as measured by increasing serum creatinine (mg/dL) (Figure 1) and decreasing GFR_{CKD-EPI}. However, differential decreases in kidney function across ART groups were not observed during

coamphotericin and tenofovir administration. From baseline through 14 days of cryptococcal meningitis therapy, there were no differences in creatinine (F-test $P=0.32$) or $GFR_{CKD-EPI}$ (F-test $P=0.62$) across ART groups. Rates of creatinine clearance (F-test interaction $P=0.45$) or and changes in $GFR_{CKD-EPI}$ (F-test interaction $P=0.37$) were similar. At the end of amphotericin induction therapy, median creatinine was 1.08 (IQR, 0.87-1.31; 90th percentile=1.54) mg/dL for those not on ART, 0.90 (IQR, 0.80-1.48; 90th percentile=2.42) mg/dL for those on ART without tenofovir, and 1.19 (IQR, 0.80-1.59; 90th percentile=1.99) mg/dL for those on ART including tenofovir ($P=0.76$) (Table 1). Similarly, there were no differences in $GFR_{CKD-EPI}$ across ART groups at the end of amphotericin therapy ($P=0.21$) (Table 1).

At 28-days post-diagnosis, kidney function had improved relative to the end of amphotericin therapy. From the end of amphotericin therapy through 4 weeks post-diagnosis, there was a mean decrease in creatinine by -0.16 (95%CI: -0.25 to -0.06) mg/dL, and an 11.9 (95%CI: 4.7 to 19.0) mL/min/1.73m² increase in $GFR_{CKD-EPI}$. These improvements in kidney function were similar across ART groups (creatinine F-test $P=0.74$; $GFR_{CKD-EPI}$ F-test $P=0.76$). Furthermore, kidney function among 28-day survivors did not differ by ART status. At 28 days post-diagnosis, median creatinine was 0.90 (IQR, 0.70 to 1.15; 90th percentile=1.64) mg/dL for participants not receiving ART, 0.90 (IQR, 0.83 to 1.11; 90th percentile=1.34) mg/dL for participants receiving ART without tenofovir, and 0.97 (IQR, 0.76 to 1.15; 90th percentile=1.39) mg/dL for participants receiving ART including tenofovir ($P=0.88$). $GFR_{CKD-EPI}$ values at 28 days post-diagnosis also did not differ by ART status (Table 1).

Overall, however, kidney function declined from diagnosis through 28 days post-amphotericin initiation; there was a 0.25 (96%CI, 0.35-0.14) mg/dL increase in mean creatinine ($P<0.001$), and a decline in the $GFR_{CKD-EPI}$ of -27 (95%CI, -34 to -19) mL/min/1.73m² ($P<0.001$). These changes were similar regardless of tenofovir or other ART use.

No participants experienced any adverse events >Grade 3 during the first month of follow-up (Table 1), no patients received dialysis, and creatinine adverse event incidence was similar across ART groups. The competing risks model yielded cumulative 28-day creatinine adverse event incidence of 16.5% (95%CI 9.7-24.8) in participants not receiving any ART, 26.4% (95%CI 10.7-37.7) in participants receiving ART without tenofovir, and 22.1% (95%CI 11.9-34.5) in participants receiving Tenofovir-based ART Tenofovir-based ART ($P=0.44$). There was no difference in risk of Grade 2-4 adverse events among persons receiving any ART as compared with persons not receiving ART at diagnosis (Hazard Ratio = 1.49, 95%CI: 0.75 to 2.95; $P=0.25$).

During induction therapy, ART was discontinued in 4% (2/50) of participants receiving tenofovir at diagnosis and in no (0/23) participants receiving ART without tenofovir. Both participants discontinued ART at discretion of their physicians, as they had both recently started ART, and there was a concern for increased mortality from unmasking *Cryptococcus*-related IRIS.²⁷ Neither participant stopped ART for reasons related to renal function.

Patients received a median of 14 doses of amphotericin (IQR: 10, 14), which were similar across ART group ($P=0.70$). Patients received a median of 50mg/day amphotericin, which was uniform across ART groups. Among patients who experienced a $GFR_{CKD-EPI} < 45$ at any point during the induction period ($n=22$), there was no difference in amphotericin doses ($P=0.40$).

Discussion

Tenofovir and amphotericin independently cause nephrotoxicity,^{6-10,14-18} and prior research indicates that risk increases when nephrotoxic drugs are co-administered.¹⁰⁻¹² Our study examined whether amphotericin B, and tenofovir co-administration of was associated with increased rates of kidney injury.

We observed some degree of amphotericin B-related nephrotoxicity in 16-26% of participants; however, after completing 14 days of amphotericin B therapy, median creatinine was similar across the three ART groups at 2 and 4 weeks post-diagnosis. We observed that decreases in kidney function were mostly transient, although average creatinine was elevated relative to diagnosis at 28 days (and $GFR_{CKD-EPI}$ decreased). These results agree with previous studies investigating amphotericin B-related nephrotoxicity.^{6,9,11,12}

We did not observe excess nephrotoxicity among persons receiving tenofovir. This supports the conclusions of Trejitnar *et al*, which postulated that amphotericin and tenofovir co-administration would likely not cause a multiplicative decline in kidney function in a clinical setting.²¹ The lack of increased creatinine following amphotericin and tenofovir co-administration could be explained by the differences in mechanisms of nephrotoxicity induced by the two drugs. Tenofovir mainly causes proximal tubular cell dysfunction, while amphotericin causes afferent arteriole vasoconstriction and direct tubular damage.^{6,7,10,15} Tenofovir-induced mitochondrial DNA depletion increases tubular dysfunction, mainly affecting the metabolic processes of kidney transport in the proximal tubules.^{15,16} Tenofovir-induced nephrotoxicity commonly presents as Fanconi syndrome with normal or reduced GFR.¹⁶ Conversely, amphotericin B deoxycholate induces acute reduction in GFR via renal afferent arteriole vasoconstriction induced by amphotericin B leads to reduced glomerular blood flow.²⁸ Second, amphotericin also has a cumulative concentration-dependent toxicity of direct injury to renal tubular epithelial cells, by forming ion-permeable pores leading to apoptosis.²⁹

Limitations of this study include its observational nature, and the small number of patients per ART group. It is possible that kidney function differences across ART groups was not detected in our study because of the overall poor health status of patients (~20% two-week mortality), and the complexity of patient management. However, we tried to account for the high mortality in this cohort analytically, via the competing risks analysis. We also used longitudinal models to characterize creatinine and GFR changes over time across groups; this allowed us to include all patients with 1 creatinine measurement, versus measures of difference, which exclude patients with incomplete follow-up. Statistical models included sex and amphotericin dose to account for potential differences in outcome associated with

those variables. This research is also strengthened by uniform management conditions, minimal loss to follow-up, and serial scheduled creatinine measurements. All patients received pre-hydration with intravenous saline prior to amphotericin, without which overall nephrotoxicity would have been worse.

In summary, amphotericin B-related nephrotoxicity remains a serious but manageable and transient problem in cryptococcal meningitis patients. Although amphotericin and tenofovir co-administration has been presumed to increase nephrotoxicity, we did not find an increased risk of kidney dysfunction greater than amphotericin alone. This study provides clinical guidance that amphotericin and tenofovir can be used together, and that mandatory switching of ART is unnecessary, provided monitoring of kidney function occurs. However, further research on the longer-term implications of amphotericin and tenofovir co-administration is needed.

Acknowledgments

This research was supported by Grand Challenges Canada (S4 0296-01), the U.S. National Institute of Neurologic Diseases and Stroke (NINDS), Fogarty International Center, and the National Institute of Allergy and Infectious Diseases (NIAID) (R01NS086312, R25TW009345, T32AI055433, U01AI089244). We thank the institutional support of Drs. Andrew Kambugu and Paul Bohjanen, and thank Dr. Wally Schlech for original conceptual discussions and his commitment to providing education regarding HIV care in Africa.

Sources of Funding: This research was supported by Grand Challenges Canada (S4 0296-01), the U.S. National Institute of Neurologic Diseases and Stroke (NINDS), Fogarty International Center, and the National Institute of Allergy and Infectious Diseases (NIAID) (R01NS086312, R25TW009345, T32AI055433, U01AI089244).

References

1. Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. *BMC Infect Dis.* 2010; 10:67. [PubMed: 20230635]
2. Cohen DB, Zijlstra EE, Mukaka M, et al. Diagnosis of cryptococcal and tuberculous meningitis in a resource-limited African setting. *Trop Med Int Health.* 2010; 15(8):910–917. [PubMed: 20573075]
3. Durski KN, Kuntz KM, Yasukawa K, Virnig BA, Meya DB, Boulware DR. Cost-effective diagnostic checklists for meningitis in resource-limited settings. *J Acquir Immune Defic Syndr.* 2013; 63(3):e101–108. [PubMed: 23466647]
4. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. *Clin Infect Dis.* 2014; 58(5):736–745. [PubMed: 24319084]
5. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med.* 2013; 368(14):1291–1302. [PubMed: 23550668]
6. Laniado-Laborin R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. *Rev Iberoam Micol.* 2009; 26(4):223–227. [PubMed: 19836985]
7. Mayer J, Doubek M, Doubek J, Horky D, Scheer P, Stepanek M. Reduced nephrotoxicity of conventional amphotericin B therapy after minimal nephroprotective measures: animal experiments and clinical study. *J Infect Dis.* 2002; 186(3):379–388. [PubMed: 12134234]
8. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clin Infect Dis.* 1998; 27(2):296–302. [PubMed: 9709879]
9. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis.* 1999; 29(6):1402–1407. [PubMed: 10585786]

10. Deray G. Amphotericin B nephrotoxicity. *J Antimicrob Chemother.* 2002; 49(Suppl 1):37–41. [PubMed: 11801579]
11. Luber AD, Maa L, Lam M, Guglielmo BJ. Risk factors for amphotericin B-induced nephrotoxicity. *J Antimicrob Chemother.* 1999; 43(2):267–271. [PubMed: 11252333]
12. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med.* 1999; 340(10):764–771. [PubMed: 10072411]
13. Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. *J Acquir Immune Defic Syndr.* 2012; 59(5):e85–91. [PubMed: 22410867]
14. Chaisiri K, Bowonwatanuwong C, Kasettrat N, Kiertiburanakul S. Incidence and risk factors for tenofovir-associated renal function decline among Thai HIV-infected patients with low-body weight. *Curr HIV Res.* 2010; 8(7):504–509. [PubMed: 21073439]
15. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Research and Treatment.* 2011; 354908
16. Perazella MA. Tenofovir-induced kidney disease: an acquired renal tubular mitochondriopathy. *Kidney Int.* 2010; 78(11):1060–1063. [PubMed: 21076445]
17. Sadre A, Munshi N, Dhande S, Dravid A. Tenofovir-induced acute kidney injury in HIV-infected patients in western India: a resource limited setting perspective. *J Int AIDS Soc.* 2012; 15(6(Suppl 4)):45–45.
18. Jose S, Hamzah L, Campbell LJ, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. *J Infect Dis.* 2014; 210(3):363–373. [PubMed: 24585896]
19. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014; 58(1):e1–34. [PubMed: 24235263]
20. Jimenez-Nacher I, Garcia B, Barreiro P, et al. Trends in the prescription of antiretroviral drugs and impact on plasma HIV-RNA measurements. *J Antimicrob Chemother.* 2008; 62(4):816–822. [PubMed: 18567912]
21. Trejtnar F, Mandikova J, Kocincova J, Volkova M. Renal handling of amphotericin B and amphotericin B-deoxycholate and potential renal drug-drug interactions with selected antivirals. *Antimicrob Agents Chemother.* 2014; 58(10):5650–5657. [PubMed: 24957831]
22. Bahr NC, Rolfes MA, Musubire A, et al. Standardized electrolyte supplementation and fluid management improves survival during amphotericin therapy for cryptococcal meningitis in resource-limited settings. *Open Forum Infect Dis.* 2014; 1(2):ofu070. [PubMed: 25734140]
23. World Health Organization. [Accessed April 1, 2015] Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2011. www.who.int/hiv/pub/cryptococcal_disease2011
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150(9):604–612. [PubMed: 19414839]
25. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA.* 2012; 307(18):1941–1951. [PubMed: 22570462]
26. U.S. Department of Health and Human Services NIOH, National Institute of Allergy and Infectious Disease. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2009.
27. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med.* 2014; 370(26):2487–2498. [PubMed: 24963568]
28. Sawaya BP, Weihprecht H, Campbell WR, et al. Direct vasoconstriction as a possible cause for amphotericin B-induced nephrotoxicity in rats. *Journal of Clinical Investigation.* 1991; 87(6):2097–2107. [PubMed: 1710234]
29. Yano T, Itoh Y, Kawamura E, et al. Amphotericin B-induced renal tubular cell injury is mediated by Na⁺ Influx through ion-permeable pores and subsequent activation of mitogen-activated

protein kinases and elevation of intracellular Ca^{2+} concentration. *Antimicrob Agents Chemother.* 2009; 53(4):1420–1426. [PubMed: 19139282]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Median (IQR) serum creatinine in persons receiving no ART (white), ART without tenofovir (light gray) and ART with tenofovir (dark gray) at meningitis diagnosis, from diagnosis through 4 weeks follow-up.

Table 1
Incidence of Grade 2, 3 and 4 Kidney Adverse Events by Baseline ART Status

	No ART		ART without tenofovir		ART with tenofovir		P-value*
	N	Median (IQR) or n (%)	N	Median (IQR) or n (%)	N	Median (IQR) or n (%)	
Creatinine Concentrations, mg/dL							
Diagnosis	75	0.68 (0.59-0.82)	21	0.63 (0.46-0.74)	42	0.64 (0.52-0.79)	0.11
7 Days	68	1.14 (0.87-1.39)	20	1.10 (0.89-1.25)	43	1.02 (0.70-1.35)	0.65
14 Days	60	1.08 (0.87-1.31)	17	0.90 (0.80-1.48)	34	1.19 (0.80-1.59)	0.76
28 Days	48	0.90 (0.70-1.15)	13	0.90 (0.83-1.11)	32	0.97 (0.76-1.15)	0.88
Glomerular Filtration Rate (GFR) mL/min/1.73m²							
GFR at Diagnosis	75		21		42		
30		0 (0.0%)		0 (0.0%)		1 (2.4%)	
30 – 44		3 (4.0%)		0 (0.0%)		0 (0.0%)	
45 – 59		1 (1.3%)		0 (0.0%)		0 (0.0%)	0.80
60 – 89		4 (5.3%)		1 (4.8%)		3 (7.1%)	
90		67 (89%)		20 (95%)		38 (90%)	
GFR at 14 Days	60		17		34		
30		0 (0.0%)		1 (5.9%)		0 (0.0%)	
30 – 44		1 (1.7%)		1 (5.9%)		3 (8.8%)	
45 – 59		4 (6.7%)		2 (12%)		4 (12%)	0.24
60 – 89		22 (37%)		3 (18%)		11 (32%)	
90		33 (55%)		10 (59%)		16 (47%)	
GFR at 28 Days	48		13		32		
30		0 (0.0%)		0 (0.0%)		0 (0.0%)	
30 – 44		1 (2.1%)		0 (0.0%)		1 (3.1%)	
45 – 59		3 (6.3%)		2 (15%)		2 (6.3%)	0.84
60 – 89		9 (19%)		1 (7.7%)		7 (22%)	
90		35 (73%)		10 (77%)		22 (69%)	

Glomerular Filtration Rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)²⁷

* Creatinine measurements compared via Kruskal-Wallis rank test; categorical variables compared via Fisher's exact test.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript