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# Risk of Nephrotoxicity in Patients With Drug-Resistant Tuberculosis Treated With Kanamycin/Capreomycin With or Without Concomitant Use of Tenofovir-Containing Antiretroviral Therapy

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**Background:** The intersection of HIV and drug-resistant (DR) tuberculosis (TB) presents the challenge of managing convergent drug toxicities.

**Methods:** We conducted a retrospective study of adult patients with DR-TB treated with a kanamycin/capreomycin-based (KM) regimen, with or without concomitant antiretroviral therapy (ART). We estimated the incidence of nephrotoxicity (defined as an increase in serum creatinine greater than 26.5  $\mu\text{mol}$ , or an increase in serum creatinine to 1.5 times the baseline value, or a decline in glomerular filtration rate to less than 60 mL/min/1.73 m<sup>2</sup>), and evaluated the association between reported drug use and nephrotoxicity using Kaplan–Meier plots.

**Results:** A total of 215 patients with DR-TB were treated with a kanamycin/capreomycin-based regimen, with or without concomitant ART. The incidence rate of nephrotoxicity was 3.6 [95% confidence interval (CI): 1.4 to 7.3], 6.9 (95% CI: 5.2 to 9.0), and 12 (95% CI: 3.3 to 30.9) cases per 100 person-months of follow-up in

the KM only group (n = 42), the KM + TDF (tenofovir disoproxil fumarate) group (n = 163), and the KM + Other ART group (n = 10), respectively. Using the KM only group as a reference, the hazard ratio was 2.06 (95% CI: 0.92 to 4.63) in the KM + TDF group, and 4.09 (95% CI: 1.17 to 14.25) in the KM + Other ART group. Advancing age was an independent predictor of nephrotoxicity (adjusted hazard ratio 1.29, 95% CI: 1.14 to 1.46).

**Conclusions:** Our findings provide evidence of a significant risk of nephrotoxicity during treatment with a kanamycin/capreomycin-based DR-TB regimen, with or without concurrent treatment with ART. This study lends further support to calls for the substitution of TDF during the intensive phase of DR-TB treatment and for close monitoring of renal function during DR-TB treatment, especially in settings where the use of kanamycin/capreomycin is unavoidable.

**Key Words:** multidrug-resistant tuberculosis, tenofovir, aminoglycoside, nephrotoxicity

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## INTRODUCTION

Tuberculosis (TB) is the leading cause of death from a curable infectious disease. Although the global burden of TB is declining, the incidence of drug-resistant TB (DR-TB) continues to rise.<sup>1</sup> South Africa has one of the highest incidence rates of multidrug-resistant TB and extensively drug-resistant TB globally, with a high rate of HIV coinfection.<sup>1</sup> In April 2010, the South African National Antiretroviral Treatment Guidelines were amended, substituting stavudine with tenofovir disoproxil fumarate (TDF) in the first-line antiretroviral therapy (ART) regimen after evidence of an improved side-effect profile.<sup>2,3</sup> An essential component of efficacious DR-TB treatment is the use of aminoglycosides (kanamycin) or polypeptides (capreomycin) during the intensive phase of treatment, for at least 6 months.<sup>4</sup> The shorter WHO-recommended multidrug-resistant TB regimen maintains the central role of an aminoglycoside during the intensive phase of treatment, albeit for a shorter period.<sup>5</sup> The concurrent treatment of HIV and TB presents the

challenge of overlapping toxicities as both aminoglycosides and TDF have the potential to result in nephrotoxicity.<sup>4,6</sup> Although early clinical trials suggest that TDF is a relatively safe drug, without significant risk of renal toxicity, some observational studies report significant renal toxicity necessitating discontinuation of the drug.<sup>7-9</sup> A systematic review demonstrated a modest but significant decline in renal function as well as an increased risk of acute kidney injury associated with TDF use.<sup>10</sup> As TDF is cleared by the proximal renal tubule, it may accumulate in the proximal tubular epithelial cells resulting in a “Fanconi-like renal tubular acidosis,” with or without progressive kidney failure.<sup>11,12</sup> The diagnostic hallmarks of Fanconi syndrome (tubular proteinuria, hyperaminoaciduria, glycosuria, and hyperphosphaturia) require urinalysis, which is uncommonly performed and reported in studies of TDF safety. The aminoglycosides have a similar propensity to accumulate in the proximal renal tubules and up to 10% of the parenteral dose may concentrate in these cells.<sup>13</sup> Here, they mediate nephrotoxic effects through inhibition of mitochondrial ribosomes, analogous to their bactericidal effect on the ribosomal units of bacteria.<sup>14</sup> Proximal tubular toxicity may be followed by progression to renal failure, particularly in the presence of hypovolemia. The serum half-life of aminoglycosides is a few hours, compared with several days in the proximal tubule cells; thus, cumulative exposure generates an exponential risk for renal toxicity. The incidence of aminoglycoside-induced nephrotoxicity is estimated at 20.6% during standard therapy for gram-negative infections, and rises to almost 50% when drug exposure exceeds 14 days.<sup>15</sup> This is of particular concern during the treatment of DR-TB, where the daily administration of an aminoglycoside occurs for at least 4 months, substantially longer than the average treatment of a gram-negative infection. A recent study, representing the only available study on the risk of nephrotoxicity in patients with DR-TB treated with a kanamycin-based regimen, demonstrated an incidence of 2.4 cases/100 person-months, 6.8

cases/100 person-months in patients who received concomitant TDF-containing ART, and 13.8 cases/100 person-years in patients on concomitant ART which did not contain TDF.<sup>16</sup>

Patients in overburdened, resource-constrained settings are subject to less stringent clinical and laboratory-based drug safety monitoring, remaining vulnerable to poor identification, triage, and management of adverse drug reactions.<sup>17</sup> Furthermore, high rates of TB/HIV coinfection mandating cotreatment with a limited formulary exposes patients to a greater risk of developing drug-associated complications compared with patients in well-resourced regions.<sup>17</sup> There is therefore an urgent need to evaluate drug-induced nephrotoxicity in DR-TB/HIV coinfecting patients in this setting. This retrospective cohort study describes the incidence of nephrotoxicity in DR-TB patients treated with a kanamycin/capreomycin-based antituberculosis regimen with or without concomitant use of a TDF-based ART regimen.

## METHODS

### Study Design, Participants, and Procedures

We conducted a retrospective study of adult patients with DR-TB who presented to a specialist DR-TB facility in KwaZulu-Natal, South Africa, within a centralized DR-TB service. Clinical and laboratory records were reviewed in patients presenting in a single month in each of 3 years (2011–2013) (Fig. 1). Using the DR-TB treatment register and the facility-based ART register, matched by facility identification number and date, we identified consecutive adult patients (≥18 years of age) with DR-TB who were initiating treatment with a kanamycin/capreomycin-based DR-TB regimen, and for whom complete clinical records were available, during the period under review. We defined 3 distinct subgroups of patients: HIV-infected patients on tenofovir-containing ART (KM + TDF group),

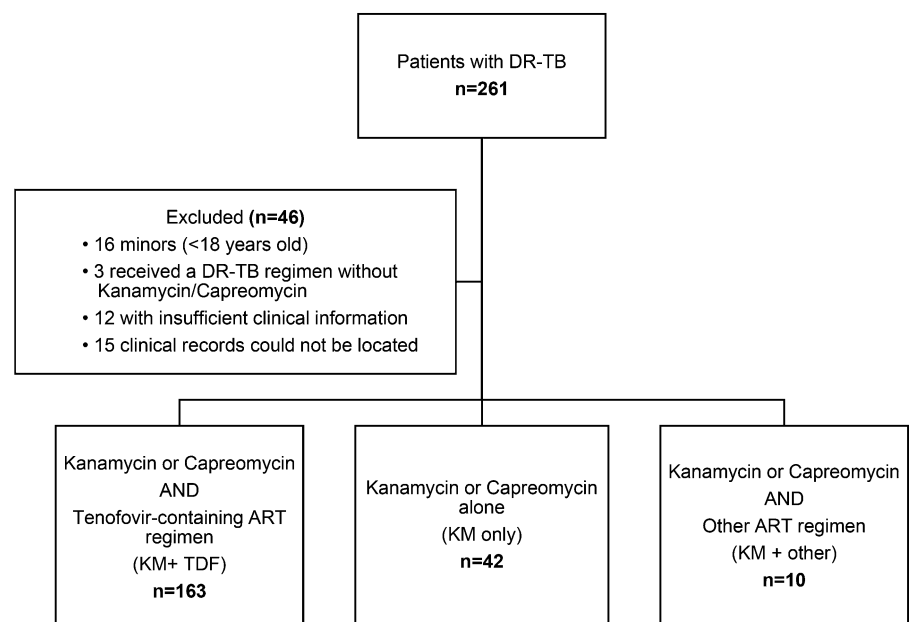


FIGURE 1. Study flow diagram.

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HIV-infected patients treated with an ART regimen that did not contain TDF (KM + Other group), and HIV-negative patients (KM only group).

All patients received standard of care at this TB facility, in which renal function [including serum creatinine and glomerular filtration rate (eGFR)] was usually monitored monthly for the duration of the aminoglycoside/polypeptide administration. DR-TB was treated with an individualized regimen, based on the *Mycobacterium tuberculosis* drug-resistance profile of the sputum sample, comprising an intensive phase, which included an injectable agent (kanamycin/capreomycin) that was administered for at least 6 months, followed by a continuation phase of oral drugs administered for approximately 18 months.<sup>18</sup> Primary drug exposure was defined as prescription of kanamycin or capreomycin according to the South African National DR-TB Policy Guidelines.<sup>18</sup> Concomitant ART was defined as the dispensing of ART along with DR-TB treatment. The dose of kanamycin or capreomycin was 15 mg/kg per day, and the standard dose of tenofovir was 300 mg per day. All drugs were secured through a centralized provincial government pharmacy, within the public health care system. Tenofovir was available as part of a fixed dose combination pill (Atrioza by Mylan, Tribuss by Aspen Pharmaceuticals, Odimmune by Cipla, or Atenef by Sonke Pharmaceuticals), kanamycin was available as vials (Bio-Kanamycin by Biotech Laboratories), and capreomycin was available as vials (Capreomycin sulfate by Mylan).

### Outcome Measures and Follow-up

Information on demographic characteristics, HIV status, TB, and laboratory safety data including renal function were collected as part of routine monitoring. Patients were followed up until the completion of the intensive phase of TB treatment heralded by the cessation of kanamycin/capreomycin, usually 6–9 months after treatment initiation.

The eGFR was estimated using the Cockcroft–Gault equation, which has been validated for use in South African black patients and is the recommended method for monitoring renal function during tenofovir and aminoglycoside use.<sup>18–20</sup> The eGFR was used as a measure of renal function and was assessed on a monthly basis. “Baseline eGFR” was taken as the most recent value before commencing the kanamycin/capreomycin. Nephrotoxicity was defined as an increase in serum creatinine greater than 26.5  $\mu\text{mol}$ , or an increase in serum creatinine to 1.5 times the baseline value, or a decline in eGFR to  $<60 \text{ mL/min/1.73 m}^2$ .<sup>16,18,20,21</sup> A single measurement crossing this threshold was considered sufficient for the definition of an event. The “Last eGFR” reflects the last available eGFR during cotreatment, usually at the end of the intensive phase of DR-TB treatment.

### Statistical Analyses

Continuous data were summarized using mean with SD or medians with interquartile range (IQR). Categorical data were summarized using percentages. The Fisher exact test or the Fisher–Freeman–Halton test was used for analysis of

categorical data, and the 2-samples *t* test, Wilcoxon rank-sum test, 1-way analysis of variance test, or Kruskal–Wallis test was used for the analysis of continuous data. Kaplan–Meier curves were constructed and the log-rank test was used to compare the cumulative probability of developing nephrotoxicity among the 3 groups. Predictors of nephrotoxicity were assessed through both univariate and multivariate proportional hazards regression. Statistical analysis was performed using SAS, version 9.4 (Statistical Analysis System, Cary, NC). All statistical tests were conducted at the 5% level of significance.

### Ethics approval

This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee of the (BE 179/10).

## RESULTS

Of a total of 261 patients who presented with DR-TB during the study period, 46 patients did not meet the criteria for inclusion into the study: 16 were under 18 years, 3 were not on kanamycin/capreomycin, 12 patients had insufficient information in their clinical records, and the clinical records of 15 others could not be located (Fig. 1).

A total of 215 patients with DR-TB were treated with kanamycin or capreomycin, with or without concomitant ART, during this study (Fig. 1). One hundred and sixty-three patients were treated with a kanamycin/capreomycin-based DR-TB regimen and TDF-containing ART (KM + TDF group), 42 HIV-negative patients were treated with a kanamycin/capreomycin-based DR-TB regimen alone (KM only group), and 10 patients were treated with a kanamycin/capreomycin-based DR-TB regimen and an ART regimen that did not contain TDF (KM + Other group). All patients in the KM + Other group received a first-line ART regimen containing efavirenz and lamivudine, together with either stavudine ( $n = 5$ ), zidovudine ( $n = 3$ ), or abacavir ( $n = 2$ ). Overall, the median age was 33 years (IQR 28–40), and was not significantly different across the groups ( $P = 0.681$ ). Table 1 Female patients comprised 48.4% of the entire cohort, with a significantly lower proportion of women in the KM only and KM + Other groups ( $P = 0.025$ ). There were no significant differences in body weight ( $P = 0.22$ ) or body mass index ( $P = 0.159$ ) across the groups. The median CD4 cell count ( $P = 0.928$ ) and the proportion of patients with a suppressed viral load ( $P = 1$ ) were not significantly different between the KM + TDF and KM + Other groups. Over 80% of patients in the entire cohort received kanamycin as the injectable agent in their DR-TB regimen, with no significant difference across groups ( $P = 0.15$ ). Patients were followed up for a median of 6.6 months (IQR 5.6–7.8) in the KM + TDF group, 6.4 months (IQR 5.5–7.3) in the KM only group, and 5.3 months (IQR 4.7–5.7) in the KM + Other group ( $P = 0.024$ ). At baseline, the median eGFR values in the KM + TDF group (84.7 mL/min/m<sup>2</sup>, IQR 68.9–100.8), the KM only group (78 mL/min/m<sup>2</sup>, IQR 69.1–94.4), and the KM + Other group (74.5 mL/min/m<sup>2</sup>, IQR 70.8–93.1) were not

significantly different ( $P = 0.61$ ). The median decline in eGFR at the end of the intensive phase of DR-TB treatment for the KM + TDF group ( $-4.6$  mL/min/m<sup>2</sup>, IQR  $-21.9$  to  $16$ ), the KM only group ( $-1.6$  mL/min/m<sup>2</sup>, IQR  $-21.8$  to  $20.2$ ), and the KM + Other group ( $-11.4$  mL/min/m<sup>2</sup>, IQR  $-24.2$  to  $32$ ) were not significantly different. Nephrotoxicity occurred in 32.5% (53/163) of patients in the KM + TDF group, 16.7% (7/42) of the KM only group, and 40% (4/10) of the KM + Other group. The incidence rate of nephrotoxicity was 6.9 [95% confidence interval (CI): 5.2 to 9.0] cases per 100 person-months of follow-up in the KM + TDF group, 3.6 (95% CI: 1.4 to 7.3) cases per 100 person-months of follow-up in the KM only group, and 12 (95% CI: 3.3 to 30.9) cases per 100 person-months of follow-up in the KM + Other group. The Kaplan–Meier curves demonstrate divergence of the curves within 60 days from treatment initiation, but no significant difference between the groups at the end of follow-up (log-rank  $P = 0.095$ ). Using the KM only group as a reference, the hazard ratio (HR) in the KM + TDF group was 1.86 (95% CI: 0.85 to 4.1) and 3.65 (95% CI: 1.07 to 12.47) in the KM + Other group. Table 2 In the multivariable proportional hazards regression model, controlling for the effects of age, sex, and baseline eGFR, the adjusted HR was 2.06 (95% CI: 0.92 to 4.63) in the KM + TDF group and 4.09 (95% CI: 1.17 to 14.25) in the KM + Other group. Age was an independent predictor of nephrotoxicity [adjusted hazard ratio (aHR) 1.29, 95% CI: 1.14 to 1.46] (Fig. 2).

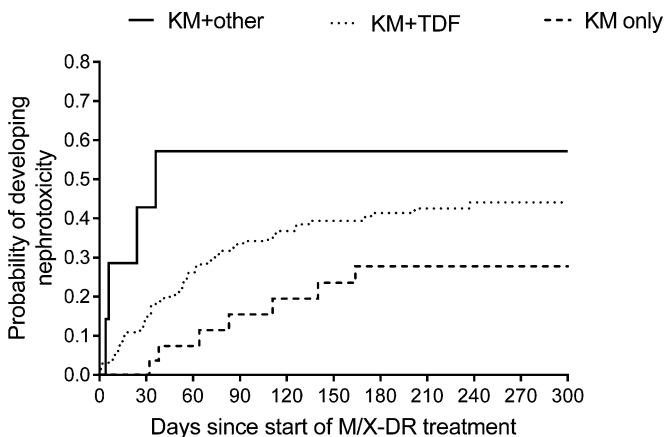
**DISCUSSION**

This is the largest study to report the incidence of nephrotoxicity in DR-TB/HIV coinfecting patients on concomitant treatment with TDF and a kanamycin/capreomycin-based DR-TB regimen. This study demonstrated a high incidence of nephrotoxicity in this South African cohort of predominantly young, black patients. Nephrotoxicity occurred in 32.5% (53/163) of patients in the KM + TDF group, 16.7% (7/42) of the KM only (HIV-negative) group, and 40% (4/10) of the KM + Other group. These figures are alarming, given the growing burden of DR-TB, especially in

high TB/HIV burden settings, where injectable agents are likely to remain an essential component of DR-TB regimens. In a study of patients with DR-TB on a kanamycin-based regimen in Namibia, similar incidence rates of nephrotoxicity were documented.<sup>16</sup> Consistent with that study, we found no statistically significant difference in the rates of nephrotoxicity between patients in the exclusively HIV-negative KM only group and the KM + TDF group, although the KM + TDF group had a nonsignificantly increased hazard of nephrotoxicity (aHR 2.06 95% CI: 0.92 to 4.63). The significantly increased hazard of nephrotoxicity (aHR 4.09 95% CI: 1.14 to 14.25) in patients in the KM + Other group seems to be a similarly consistent finding with the Namibian study. The incidence of nephrotoxicity in the KM only group is substantially higher than was previously reported in a study of HIV-negative patients with DR-TB in which 4% of their cohort experienced aminoglycoside-related nephrotoxicity after 6 months of treatment.<sup>22</sup>

The nephrotoxic potential of aminoglycosides is well-documented, but a paucity of data exists regarding their specific use in the treatment of DR-TB, which requires a substantially longer treatment duration than most other indications.<sup>22,23</sup> The initial concerns about TDF-induced nephrotoxicity arose out of compelling evidence of the nephrotoxic potential of other nucleotide transcriptase inhibitors.<sup>24</sup> Despite early clinical trials demonstrating the safety of TDF, especially regarding renal toxicity, concern for the risk of kidney injury has persisted.<sup>25–33</sup> An analysis of the FDA-reported adverse events registry revealed 164 cases of proximal tubule injury between 2001 and 2006.<sup>34</sup> The risk of acute renal failure was estimated as 0.7% (95% CI: 0.2 to 1.2) higher in TDF-exposed patients compared with patients on ART without TDF in a meta-analysis including 7486 patients from 8 studies.<sup>10</sup> Importantly, most studies of TDF excluded patients with preexisting kidney disease, as well as patients on nephrotoxic agents. A retrospective cohort study in South Africa revealed an increased risk of TDF-induced nephrotoxicity in patients with mild (HR 4.8; 95% CI: 1.5 to 15.2) or moderate (HR 15.0; 95% CI: 3.4 to 66.5) kidney dysfunction at the start of treatment.<sup>35</sup> Of the patients in the KM + TDF group who experienced nephrotoxicity in our study, 11 patients required substitution of TDF after the episode of nephrotoxicity, but no patients died or required renal replacement therapy.

We found the highest risk of nephrotoxicity in patients cotreated with kanamycin and a non-TDF-containing ART regimen (KM + Other), even after taking CD4 count and HIV virological suppression into account. This is possibly due to confounding by contraindication of TDF. Although baseline eGFR in the KM + Other group was not significantly different to the other 2 groups, it is possible that physicians identified these patients as being at risk of kidney injury and therefore deliberately avoided prescribing TDF. In addition, patients who were already on a non-TDF-containing ART regimen at the initiation of DR-TB treatment could have had TDF substituted out of the regimen during a previous episode of nephrotoxicity and would have remained at risk of nephrotoxicity.<sup>36</sup> These explanations are supported by the finding that all patients on a non-TDF-containing ART regimen in this study remained on



**FIGURE 2.** Kaplan–Meier curve for cumulative probability of developing nephrotoxicity.

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a first-line ART regimen containing either stavudine, zidovudine, or abacavir instead of TDF.

The incidence of nephrotoxicity, based on this and the previous study by Sagwa et al<sup>16</sup> in Namibia, in this vulnerable group of patients is unacceptably high, and is especially worrying in the developing world setting. Although it is well known that patients of African descent are at greater risk of both acute kidney injury and progression to chronic kidney disease, it remains unclear whether the incidence rate seen in this exclusively black African cohort exposed to a significant nephrotoxic burden is higher than would have been seen in other populations.<sup>37</sup> In HIV-negative patients, chronic kidney disease remains 4 times more frequent in Africa than in industrialized countries.<sup>38</sup> In high HIV burden settings such as South Africa, people living with HIV bear a 10% lifetime risk of developing kidney disease, considerably higher than the already elevated risk in HIV-negative individuals of African descent.<sup>39</sup> The increased risk of chronic kidney disease in this population makes the risk of an acute kidney injury, even if reversible, more concerning as the risk of progression to chronic kidney disease has been clearly associated with previous episodes of acute kidney injury.<sup>36,40</sup> Although no patients died or required renal replacement therapy during the study period, a long-term follow-up study design will be required to respond to this concern definitively, and to define the risk of chronic kidney disease in patients who experience nephrotoxicity during treatment with kanamycin/capreomycin-based regimens for DR-TB, with or without concomitant ART exposure. The cost of renal support, in the way of acute or chronic renal replacement therapy, is high, which has limited the availability of these resources in most of sub-Saharan Africa. With scarcity of nephrology care facilities, the lack of skilled personnel, and the high cost associated with kidney failure, prevention of kidney disease is critical. In addition, HIV-infected patients

remain largely excluded from available state-funded renal replacement therapy programs.<sup>41</sup> The inability to appropriately care for patients who develop nephrotoxicity after an iatrogenic nephrotoxic exposure should weigh heavily on the balance of risks and benefits of using such agents in the care of patients with DR-TB/HIV, who represent some of the most vulnerable individuals in our setting.

The current recommendations for dealing with the dual nephrotoxic drug exposure in the treatment of DR-TB/HIV include continuing TDF with fortnightly renal function assessments, or switching to abacavir or zidovudine for the duration of DR-TB injectable use. The practicality of such close biochemical monitoring in the former scenario is doubtful in a resource-poor, high TB/HIV burden setting. Substitution of TDF with tenofovir alafenamide may be a reasonable alternative, given early evidence of improved renal safety and possible benefit in patients with renal impairment.<sup>42</sup> In patients who are ART-naive, initiation of an abacavir or zidovudine-based regimen is recommended for the duration of DR-TB injectable use, with a switch to TDF thereafter. In settings where bedaquiline is available, its use may be favored over an aminoglycoside/polypeptide, provided that hepatic function is normal, the patient has no significant risk factors for the development of hepatotoxicity, and there is no evidence of QT interval prolongation on electrocardiography.

Individualized pharmacokinetic guided dosing of aminoglycosides has been shown to be a cost-effective strategy for reducing the incidence of nephrotoxicity in the treatment of gram-negative infection, but requires intensive pharmacokinetic profiling every 72 hours. The practicality and cost-effectiveness of this strategy needs further evaluation in a resource-constrained setting and in the context of prolonged aminoglycoside use. The use of extended dosing intervals for aminoglycosides is an area of potential future research, and

**TABLE 1.** Baseline and Follow-up Characteristics of Patients With DR-TB

Variable	KM + TDF (N = 163)	KM Only (N = 42)	KM + Other (N = 10)	P
Baseline				
Age(yr), median (IQR)	33.0 (28.0–39.0)	31.5 (24.0–45.0)	35.0 (31.0–46.0)	0.681
Female, % (n)	53.4% (87)	35.7% (15)	20.0% (2)	0.025
Weight(kg), median (IQR)	55.7 (48.7–62.7)	57.3 (50.0–70.0)	55.3 (47.0–57.7)	0.220
Body mass index (kg/m <sup>2</sup> ), median (IQR)	20.3 (17.9–23.0)	21.3 (18.6–28.7)	19.4 (17.7–20.4)	0.159
eGFR (mL/min/1.73 m <sup>2</sup> ), median (IQR)	84.7 (68.9–100.8)	78.0 (69.1–94.4)	74.5 (70.8–93.1)	0.610
CD4 <sup>+</sup> count (cells/mm <sup>3</sup> ), median (IQR)*	183.0 (100.9–328.0)	—	212.0 (64.0–264.0)	0.928
Patients with undetectable viral load, % (n)†	59.4% (38)	—	66.7% (2)	1.00
Nephrotoxic agent, % (n)				
Capreomycin	14.1% (23)	4.8% (2)	20.0% (2)	0.150
Kanamycin	85.9% (140)	95.2% (40)	80.0% (8)	
Follow-up				
Months on DR-TB treatment, median (IQR)	6.6 (5.6–7.8)	6.4 (5.5–7.3)	5.3 (4.7–5.7)	0.024
Last eGFR (mL/min/1.73 m <sup>2</sup> ), median (IQR)	78.1 (64.0–100.5)	84.5 (63.9–100.0)	65.2 (48.3–105.2)	0.778
Median (IQR) change in eGFR (last eGFR–baseline eGFR)	–4.6 (–21.9–16.0)	–1.6 (–21.8–20.2)	–11.4 (–24.2–32.0)	0.790

\*Patients with missing data: 40.

†Patients with missing data: 106.

**TABLE 2.** Factors Associated With Nephrotoxicity

Variable	HR (95% CI)	P	aHR (95% CI)	P
Baseline eGFR (per 50 mL/min/1.73 m <sup>2</sup> increase)	1.00 (0.59 to 1.69)	1.00	1.24 (0.73 to 2.08)	0.425
KM only	1.0			
KM + TDF	1.86 (0.85 to 4.10)	0.122	2.06 (0.92 to 4.63)	0.081
KM + Other	3.65 (1.07 to 12.47)	0.039	4.09 (1.17 to 14.25)	0.027
Age (per 5-year increase)	1.24 (1.12 to 1.38)	<0.0001	1.29 (1.14 to 1.46)	<0.0001
Female	1.0			
Male	0.89 (0.55 to 1.45)	0.641	0.84 (0.51 to 1.39)	0.502

should be directed toward identifying the longest possible dose interval that preserves drug efficacy. Fortunately, aminoglycosides exhibit concentration-dependent killing activity with a strong postantibiotic effect, making them good candidates for a drug-free interval that would allow for degradation of accumulated drug within the proximal tubule epithelium while preserving ongoing bacterial killing activity.<sup>43</sup>

Our study supports the finding that the nephrotoxic burden from DR-TB injectable use is substantial and that the avoidance of an additive nephrotoxic burden may be prudent. It remains biologically plausible that toxicities of TDF and aminoglycosides/polypeptides may be additive at the level of the proximal renal tubules, and that their concomitant use may predispose patients to the development of kidney injury. In the TDF Expanded Access Programme, including 10,343 patients, concomitant nephrotoxic drug exposure was independently associated with a significant increase in serum creatinine (odds ratio 2.4 95% CI: 1.08 to 5.34).<sup>44</sup>

As the primary site of insult in the use of both TDF and aminoglycosides/polypeptides has been identified as the proximal tubule of the nephron, we recommend regular monitoring for tubular nonalbumin proteinuria, normoglycemic glycosuria, hyperphosphaturia, hyperuricosuria, and aminoaciduria. Importantly, tubular (nonalbumin) proteinuria often escapes detection by routine urine dipstick analysis, as the dipstick primarily detects urine albumin. Measurement of urine albumin and urine protein has been demonstrated to be an inexpensive test for the detection of tubular proteinuria, which is characterized by a low urine albumin-to-protein ratio.<sup>45</sup> The use of this spot urine evaluation is both practical and reliable for the detection of proximal tubular injury in a resource-poor setting but, like in this study setting, remains underutilized.<sup>16,46</sup>

This study represents the largest reported cohort of patients with DR-TB/HIV on concurrent TDF and injectable DR-TB drugs. Nonetheless, we recognize several noteworthy limitations. The size of the “KM + Other” subgroup was small, and the results of the study need to be interpreted with the necessary prudence. There were no data on adherence or drug concentrations used to qualify drug exposure, and it is possible that true drug exposures are not accurately represented. However, poor adherence would have resulted in an underestimation of nephrotoxicity, and would therefore not detract from the key finding of high rates of nephrotoxicity in all study groups. This was a retrospective study under programmatic conditions, and the monitoring of renal function was neither

protocolled nor standardized. In addition, as with the only other study on this subject, urinalysis was not routinely performed, and we were therefore unable to report on features of proximal renal tubule injury in this cohort.<sup>16</sup> We had no information on HIV-associated kidney disease; however, the rate of nephrotoxicity was similarly high in patients who were HIV-negative as those with HIV. It is possible that patients with HIV who were on a non-TDF-containing regimen might have had previous kidney insults, but it is unlikely that these patients would have had a systematically increased risk of HIV-associated kidney disease compared with the patients on a TDF-containing regimen as baseline kidney function was not significantly different between these groups. In the absence of a consensus definition of nephrotoxicity in this context, this study used a composite definition of nephrotoxicity encompassing the 3 most widely used criteria for the diagnosis. In doing so, more cases of nephrotoxicity may have been identified than if only a single criterion was used. Using a decline in eGFR to <60 mL/min/m<sup>2</sup> as the only threshold, as was done in other similar studies, this study would have identified 14 (of 64) fewer cases of nephrotoxicity. The implications of acute kidney injury in this population are not clear, and because long-term follow-up of renal function was not performed, we are uncertain as to the risk of ongoing or progressive renal insufficiency.

**CONCLUSIONS**

Our findings provide evidence of a significant risk of nephrotoxicity during treatment with a kanamycin/capreomycin-based DR-TB regimen, with or without concurrent treatment with ART. There was a modestly increased incidence of nephrotoxicity during concomitant TDF exposure, although the effect was more pronounced in patients cotreated with KM-Other ART. This study lends further support to calls for the substitution of TDF during the intensive phase of DR-TB treatment and for close monitoring of renal function during DR-TB treatment, especially in settings where the use of kanamycin/capreomycin is unavoidable.

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