Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents

Article *in* The International Journal of Tuberculosis and Lung Disease · December 2017

DOI: 10.5588/ijtld.16.0953

CITATIONS
5

READS
60

8 authors, including:

Evans Sagwa
Utrecht University
22 PUBLICATIONS **306** CITATIONS
SEE PROFILE

Nunurai Ruswa
Independent Researcher
12 PUBLICATIONS **214** CITATIONS
SEE PROFILE

Timothy Rennie
67 PUBLICATIONS **699** CITATIONS
SEE PROFILE

Assegid Mengistu
Independent Researcher
8 PUBLICATIONS **85** CITATIONS
SEE PROFILE

INT J TUBERC LUNG DIS 21(12):1245–1250

http://dx.doi.org/10.5588/ijtld.16.0953

Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents

E. L. Sagwa,* N. Ruswa,† F. Mavhunga,† T. Rennie,‡ A. Mengistu,§¶ T. T. Mekonen,¶ H. G. M. Leufkens,*# A. K. Mantel-Teeuwisse*

***Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; †National Tuberculosis and Leprosy Program, Ministry of Health and Social Services, Windhoek, ‡University of Namibia School of Pharmacy, Windhoek, §Operations Research and Program Monitoring, Directorate of Special Programmes, Ministry of Health and Social Services, Windhoek, ¶National HIV and STI Control Programme, Ministry of Health and Social Services, Windhoek, Namibia; #Medicines Evaluation Board, Utrecht, The Netherlands**

SUMMARY

SETTING: To compare renal insufficiency among multidrug-resistant tuberculosis (MDR-TB) patients treated with kanamycin (KM) based regimens and those treated concomitantly with tenofovir disoproxil fumarate (TDF) or other antiretroviral therapy (ART) regimens in Namibia.

DESIGN: Retrospective review of the treatment records and laboratory tests of patients initiated on MDR-TB treatment (January–December 2014). The glomerular filtration rates (eGFR) estimated pre- and post-treatment were compared using the analysis of variance test. Renal insufficiency was defined as an eGFR of <60 ml/min/1.73 m^2. Use of KM or TDF and association with renal insufficiency was assessed using Kaplan-Meier plots and Cox proportional hazards analysis.

RESULTS: The baseline mean eGFR for the three groups was similar ($P = 0.24$): 139.3 ± 25.6 ml/min for the KM group ($n = 68$), 131.1 ± 25.7 ml/min for the KM+TDF group ($n = 44$) and 134.2±34.4 ml/min for the KM+Other group ($n = 23$). After 8 months, the values had declined significantly to respectively 104.8 ± 37.5 ml/min ($P < 0.001$), 101.5 ± 38.3 ml/min ($P < 0.001$) and 111.5 ± 41.7 ml/min ($P = 0.01$). Co-treatment with KM+ART was associated with an increased risk of renal insufficiency (hazard ratio [HR] 1.8, 95%CI 0.7–4.1, $P = 0.20$ for KM+TDF, and HR 3.5, 95%CI 1.4–8.2, $P = 0.005$ for KM+Other ART).

CONCLUSION: Renal function declined at a similar rate in MDR-TB patients treated with KM-based regimens compared with patients treated concomitantly with TDF-based or other ART. The risk of renal insufficiency was greater for patients on ART.

KEY WORDS: nephrotoxicity; TB-HIV co-infection; aminoglycosides; nucleoside reverse transcriptase inhibitors; Namibia

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) and human immunodeficiency virus (HIV) infection are prevalent in many low- and middle-income countries (LMICs) where they increasingly affect the same person.[1,2] Patients co-infected with MDR-TB and HIV require complex treatment regimens that comprise multiple anti-tuberculosis and antiretroviral (ARV) medicines.[3] These medicines are taken for long periods of time, potentially increasing the risk of adverse effects, especially if treatment regimens are administered concomitantly.[4]

The majority of LMICs use a public health approach for the treatment of MDR-TB and HIV, in which standard regimens that constitute combinations of recommended medicines are administered to large numbers of patients.[5–7] In 2014, kanamycin (KM) was the recommended aminoglycoside for the intensive phase of MDR-TB treatment in Namibia, in combination with a minimum of four other anti-tuberculosis drugs.[8] Tenofovir disoproxil fumarate (TDF), a nucleotide analogue ARV used in combination with lamivudine (3TC) and efavirenz (EFV), used to be the recommended first-line antiretroviral therapy (ART) for the treatment of HIV infection.[9] KM and TDF are generally well tolerated, but acute renal failure is a potential adverse effect of both medicines.[10,11] This limits their simultaneous use in patients with MDR-TB and HIV infection, as the concomitant use of KM and TDF raises the clinical concern of possible additive drug-induced nephrotoxicity.[4] Clinicians and national treatment guidelines have therefore cautioned against the concomitant administration of aminoglycosides and TDF.[8,12] However, published data from real-life programmatic experience about the concurrent use

Correspondence to: Evans L Sagwa, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, PO Box 80082, 3508 TB Utrecht, The Netherlands. e-mail: esagwa@gmail.com
Article submitted 30 December 2016. Final version accepted 13 August 2017.

of these two drugs to guide clinicians on how best to manage patients treated concomitantly with regimens containing both KM and TDF are limited.

The aim of the current study was to compare renal function and the incidence of renal insufficiency among patients treated with standard KM-based MDR-TB regimens with those treated concomitantly with standard TDF-based or other ART regimens for HIV in Namibia.

METHODS

Study population and study design

This was a retrospective follow-up study using linked electronic treatment and laboratory patient records. All patients treated for MDR-TB between 1 January and 31 December 2014 at Namibia's public health facilities and whose records were available in the electronic MDR-TB treatment register, in the ARV dispensing register (in the case of HIV-infected patients) and in the national laboratory database were included in the study. These data sets contained records of patients who were consecutively enrolled for MDR-TB treatment, those treated for HIV, and the biomedical tests performed. The patients were followed up after being on MDR-TB treatment for at least 7 days. The study end points included diagnosis of renal insufficiency, death or 8 months after start of treatment. Patients who were lost to follow-up or who transferred out without reaching one of the three endpoints were administratively censored and contributed to patient follow-up times up to the last date of their follow-up.

Linkage of medical records and data collection

Electronic patient records in the MDR-TB treatment database, the medical laboratory tests database and the HIV treatment database were linked using LinkPlus® software (Centers for Disease Control and Prevention, Atlanta, GA, USA; http://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm), as described in detail by Corbel et al.[13] The final data set for analysis contained the patients' demographic data, baseline and follow-up serum creatinine data, and information about MDR-TB and HIV treatment. Time since the start of MDR-TB treatment was denoted in days. The number of days was then transformed into months of follow-up.

Definition of medicine exposure

Primary drug exposure was defined as the prescription of KM according to the Namibian MDR-TB treatment guidelines. Concomitant ART exposure was defined as the dispensing of TDF or other ARVs along with MDR-TB treatment. The usual prescribed dose of KM was 15 mg per kg body weight per day,[8] while the standard dose of TDF was 300 mg per day.[9] KM was administered for the duration of the intensive phase of MDR-TB treatment (which lasted 8 months), whereas TDF use is life-long unless otherwise changed or stopped by the attending physician or abandoned by the patient. The standard MDR-TB regimens for the intensive phase of treatment comprised KM, cycloserine, ethionamide, levofloxacin and pyrazinamide, and sometimes ethambutol.[8] TDF was co-prescribed with 3TC and EFV or nevirapine for HIV.[9] The use of other reverse-transcriptase inhibitor nucleoside analogues such as zidovudine (AZT) and stavudine (D4T) was also recorded. The duration that a patient had been on ART at the time of MDR-TB treatment initiation was also established.

Study endpoint

The primary endpoint of our study was the occurrence of renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2. eGFR values were calculated from serum creatinine levels of patients using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units-ckd-epi.asp). The CKD-EPI equation does not require the body weight of the patient because the results are normalised to 1.73 m^2 body surface area, which is the accepted average surface area for an adult.[14]

Statistical analysis

Patients' baseline characteristics were summarised using means ($\pm$ standard deviations), medians, interquartile ranges (IQRs) and proportions. The χ^2 test and the Kruskal-Wallis test were used to assess whether categorical variables differed significantly. Mean eGFR values were compared before and after the start of MDR-TB treatment and between the two treatment groups using a two-way analysis of variance (ANOVA). Kaplan-Meier survival analysis and the log-rank test were performed to compare the cumulative incidence of renal insufficiency in each group. Cox proportional hazards analysis was used to calculate the hazard ratios (HRs) associated with the occurrence of renal insufficiency during follow-up. $P < 0.05$ was considered statistically significant.

All statistical analyses were performed using Epi Info™ v7.1.3.3 (US Centers for Disease Control and Prevention, Atlanta, GA, USA), Microsoft Excel® 2003 (Microsoft Corporation, Redmond, WA, USA) and EZR v1.32 (R Project for Statistical Computing, Vienna, Austria).[15]

Ethics statement

The study protocol was approved by the Institutional Review Board of Utrecht University, Utrecht, The Netherlands (reference: UP1307) and the research and ethics committee of the Namibian Ministry of

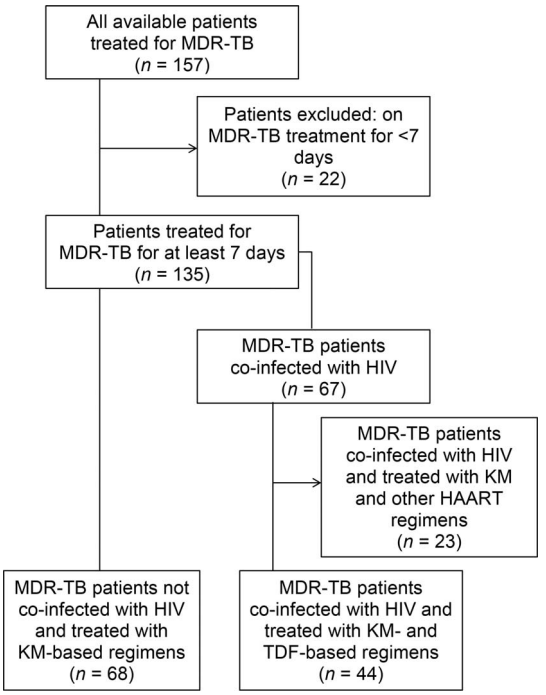

Figure 1 Study flowchart. MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus; KM = kanamycin; HAART = highly active antiretroviral therapy; TDF = tenofovir.

Health and Social Services, Windhoek, Namibia (reference: 17/3/3).

RESULTS

Of the 157 patient records retrieved from the MDR-TB treatment register, 135 met the inclusion criteria for our study (Figure 1). Sixty-eight patients were treated with KM-based regimens alone (KM group); 44 were co-treated with KM plus TDF-based ART (KM+TDF group), whereas 23 were co-treated with KM plus AZT or D4T-based ART (KM+Other group). The overall mean age was 34.8 ± 12.9 years, and was not significantly different across the three groups ($P = 0.25$). The proportion of males in all three groups was similar ($P = 0.20$). Patients were followed up for a median of 213 days (IQR 150–240) from the time they initiated MDR-TB treatment. The duration of follow-up was not significantly different ($P = 0.10$) across the treatment groups (Table 1). Testing for serum creatinine tended to be more frequent among HIV co-infected persons (median 10 and 12 tests, respectively) compared with a median of four tests among non-infected persons ($P < 0.01$).

At baseline (i.e., at the start of MDR-TB treatment), the 67 patients on HIV treatment had been on ART for a median of 4.0 years (IQR 3.0–6.5). Those on TDF-based regimens had been on ART for a significantly shorter length of time than those on AZT/D4T-based regimens (median 3.5 years, IQR 2.0–5.5 vs. median 7.0 years, IQR 5.0–9.0, $P < 0.01$).

There was an overall gradual decline in renal function (Figure 2). At the start of KM treatment, the mean baseline eGFR values in the KM group (139.3 ± 25.6 ml/min), in the KM+TDF group (131.1 ± 25.7 ml/min) and in the KM+Other group (134.2 ± 34.4 ml/min) were not significantly different ($P = 0.24$). After 8 months of follow-up, mean eGFR values had significantly declined to 104.8 ± 37.5 ml/min in the KM group ($P < 0.001$), 101.5 ± 38.3 ml/min in the KM+TDF group ($P < 0.001$) and to 111.5 ± 41.7 ml/min in the KM+Other group ($P = 0.01$) (Table 2).

Kaplan-Meier curves indicated that the difference in the incidence of renal insufficiency across the three treatment groups (log-rank test, $P = 0.009$) was statistically significant (Figure 3). Kaplan-Meier curves for the KM+TDF group and KM+Other group were close to each other, especially within the first 150 days of follow-up, but diverged from the KM-only curve. The incidence of renal insufficiency was 2.4 cases/100 person-months of follow-up in the KM-only group, 6.8 in the KM+TDF group and 13.8 in the KM+Other group. Using the KM-only group as reference, the hazard ratio (HR) in the KM+TDF

Table 1 Baseline characteristics of patients

Characteristic	KM group ($n = 68$) median [IQR]	KM+TDF ($n = 44$) median [IQR]	KM+Other* ($n = 23$) median [IQR]	*P* value
Age, years, mean ± SD	33.8 ± 12.8	37.7 ± 13.4	37.0 ± 10.4	0.25†
Males, *n* (%)	46 (67.6)	23 (52.3)	16 (69.6)	0.20‡
Follow-up, days	220 [150–240]	213 [150–240]	200 [146–240]	0.10§
Serum creatinine tests/person	4 [2–7]	10 [6–15]	12 [6–20]	<0.01§
Baseline serum creatinine, mmol/l, mean ± SD	63.7 ± 22.7	64.4 ± 17.6	66.2 ± 21.5	0.88†
Baseline creatinine clearance, ml/min, mean ± SD	139.3 ± 25.6	131.1 ± 25.7	134.2 ± 34.4	0.24†
Time on antiretroviral treatment, years	NA	3.5 [2–5.5]	7 [5–9]	<0.01§

* This subgroup comprises 23 HIV co-infected patients on AZT or D4T-based HAART. Other antiretroviral agents in the AZT-or D4T-based HAART regimens were lamivudine, efavirenz, nevirapine and lopinavir/ritonavir.
† ANOVA test.
‡ χ^2 test.
§ Kruskal-Wallis test.
KM = kanamycin; TDF = tenofovir; IQR = interquartile range; SD = standard deviation; NA = not applicable; HIV = human immunodeficiency virus; AZT = zidovudine; D4T = stavudine; HAART = highly active antiretroviral therapy; ANOVA = analysis of variance.

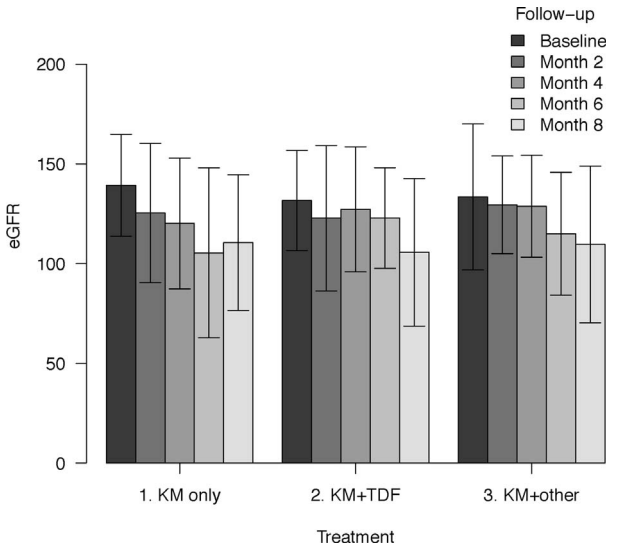

Figure 2 Renal function over time, disaggregated by patient treatment group. eGFR = estimated glomerular filtration rates; KM = kanamycin; TDF = tenofovir.

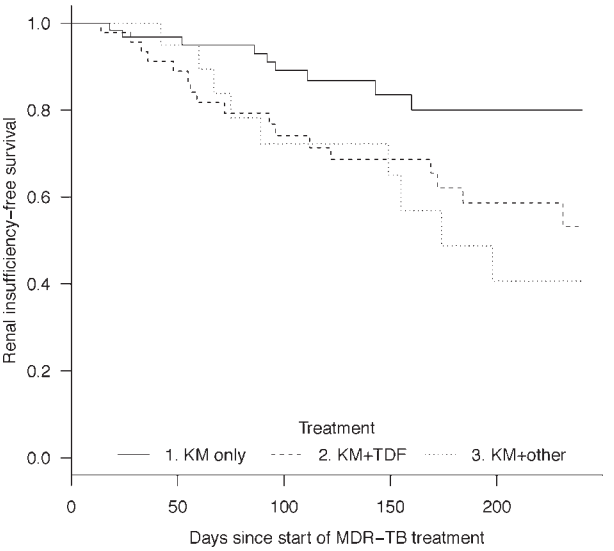

Figure 3 Kaplan-Meier curves comparing the renal insufficiency-free survival of patients according to treatment regimen. KM = kanamycin; TDF = tenofovir; MDR-TB = multidrug-resistant tuberculosis.

group was 2.1 (95% confidence interval [CI] 0.9–4.7, and 3.6 (95%CI 1.5–8.6) in the KM+Other group. After adjustment for age, the HRs were respectively 1.8 (95%CI 0.7–4.1) and 3.5 (95%CI 1.4–8.2) (Table 3). Age was not a confounder but an independent risk factor.

DISCUSSION

We observed an overall statistically significant decline in renal function over time during the intensive phase of MDR-TB treatment using standard KM-containing regimens, with or without concomitant ART. This decline occurred at a similar rate in non-HIV-infected patients treated with KM-based regimens alone compared with HIV co-infected patients treated concomitantly with KM+TDF or with KM+Other ARVs. However, HRs revealed an increased, albeit not statistically significant, risk of renal insufficiency when KM+TDF were taken together during the intensive phase of MDR-TB treatment. The risk of renal insufficiency was more clearly significantly increased in patients co-treated with KM+Other ARVs. Incidence rates clearly showed a more pronounced risk gradient across the three groups.

The loss of renal function in patients treated with KM or other aminoglycosides is not a new finding. It has been unequivocally established that KM and other aminoglycosides used in MDR-TB treatment are nephrotoxic.[16–18] TDF has also been shown to be nephrotoxic. TDF damages the renal proximal tubular cells, causing defective (re)absorption of solutes from the renal tubules, thereby resulting in a Fanconi-like syndrome or severe acute tubular necrosis.[19,20] The reason why the time-course of decline in renal function seemed to be comparable in the KM-only and KM+TDF or KM+Other groups during follow-up could be related to possible similarities in the pathophysiological mechanisms underlying the nephrotoxicity caused by the two drugs.[21,22] This hypothesis needs to be further verified through comparative biomolecular studies of the nephrotoxic mechanisms of KM and TDF.

HIV co-infected MDR-TB patients in our cohort were mostly treatment-experienced, having been on ART for a median period of about 4 years at the time of initiating MDR-TB treatment. Those treated concomitantly with AZT or D4T-based regimens tended to have been on ART twice as long as those treated with TDF-based ART regimens. This is because AZT or D4T were adopted for ART in the

Table 2 Renal function by MDR-TB treatment group before and after follow-up

	Before (baseline mean eGFR) ml/min	After (mean eGFR after 8 months) ml/min	Within-group difference in mean eGFR	*P* value
KM only group	139.3 ± 25.6	104.8 ± 37.5	34.0	<0.001
KM+TDF group	131.1 ± 25.7	101.5 ± 38.3	29.6	<0.001
KM+Other group*	134.2 ± 34.4	111.5 ± 41.7	22.7	0.01
Between-group difference in mean eGFR (*P* value)	0.24	0.20		

* The Other group was treated with zidovudine or stavudine-based regimens.
MDR-TB = multidrug-resistant tuberculosis; eGFR = estimated glomerular filtration rates; KM = kanamycin; TDF = tenofovir.

Table 3 Factors associated with renal insufficiency

	Univariate analysis		Multivariate analysis	
Factor	HR (95%CI)	*P* value	HR (95%CI)	*P* value
KM	Reference		Reference	
KM+TDF	2.1 (0.9–4.7)	0.08	1.8 (0.7–4.1)	0.20
KM+Other	3.6 (1.5–8.6)	0.004	3.5 (1.4–8.2)	0.005
Age <45 years	Reference		Reference	
Age ⩾45 years	2.7 (1.4–5.4)	0.004	2.6 (1.3–5.2)	0.008

HR = hazard ratio; CI = confidence interval; KM = kanamycin; TDF = tenofovir.

public health sector of Namibia much earlier than TDF, in 2010.[23] We found that patients on AZT or D4T-based ART showed the greatest risk of renal insufficiency compared with the other treatment groups, even if the time period on ART was taken into account: this could have been due to confounding by contraindication.[24] TDF-containing therapy (contraindication) may deliberately not have been prescribed at baseline or early in their treatment by physicians in patients with clinical suspicion of being at risk of renal insufficiency. Such patients are more likely to be treated with AZT or D4T, the two drugs considered to be non-injurious to the kidney. Patients who may have been initially placed on TDF-based regimens and who may have subsequently developed signs of loss of renal function might have been moved to AZT-based regimens. The consequence of such therapeutic choices may have led inadvertently to channelling, whereby patients on AZT or D4T may falsely be seen as carrying a higher risk of renal insufficiency when in fact they were already predisposed to renal damage. This scenario could partly explain why the Kaplan-Meier curves for these two treatment groups were similar, especially within the first 150 days of MDR-TB treatment. Moreover, as we did not have access to patients' virological and immunological data, ascertaining whether HIV-associated nephropathy (HIVAN)[25,26] played a role became difficult. However, the pattern of renal insufficiency was similar for the two types of ART regimens during the period of concomitant KM treatment.

Epidemiologically, TDF exposure appears to cause only a modest decrease in eGFR,[27] as observed in our study and that of Hall et al., with significant impairment of glomerular function being relatively rare.[20] Antoniou et al. found that renal insufficiency was rare among their study cohort of 172 patients treated with TDF-based ART.[28] Based on the literature reviewed, TDF-associated nephrotoxicity is not treatment-limiting from a public health perspective. It would appear, therefore, that the additional risk of renal failure due to the concomitant administration of KM and TDF in a real-life programmatic setting might be less than would have been theoretically expected. However, a bigger prospective study could help to answer this question.

The main strength of our study was that it was based on data from clinical practice, reflecting the real-life context of use of the study drugs. However, several potential confounding factors were not taken into account due to lack of the required data. For example, there was no information on the use of other nephrotoxic agents, on switching antiretroviral medicines or on the immunological stage of HIV disease at initiation of treatment and later. Moreover, distinguishing between ARV-related renal toxicity from HIV-associated nephropathy was also challenging. Information on the exposure to medicines was only available as nominal variables—the use or non-use of the medicines of interest—thus preventing us from studying the quantitative dose and cumulative effect of drug exposure on renal function. Being a retrospective cohort study and not a randomised control trial, our study suffered from the common pitfalls of observational studies such as selection bias and confounding. Finally, some subgroups had few patients, thereby diminishing the statistical power of the study to detect real differences for such subgroups.

CONCLUSION

Renal function declined at similar rates among non-HIV-infected MDR-TB patients treated with standard KM-based regimens alone, compared with those who were treated concomitantly for MDR-TB and HIV coinfection with KM and TDF-based ART, or with other antiretroviral regimens. KM co-treatment with ARVs was associated with an increased risk of renal insufficiency. This risk augmentation was modest if KM was co-administered with KM+TDF, but was pronounced among patients using KM+Other ART. Clinicians need to closely monitor the renal function of MDR-TB patients on KM-based treatment, especially those treated concomitantly for HIV. Given the current important role of TDF in HIV treatment, the renal safety of the combined use of KM + TDF should be ascertained further through a sufficiently powered prospective cohort study.

Acknowledgements

Funding for this study was personally provided by ES as part of his doctoral studies. The authors thank the Permanent Secretary of the Namibian Ministry of Health and Social Services (Windhoek,

Namibia), the management of the Namibia Institute of Pathology (Windhoek), G Uuaka, S Mwinga and B Ongeri for their assistance in providing and organising study data; and S Agolory of the US Centers for Disease Control and Prevention, Atlanta, GA, USA, for reviewing the final draft of this article.

Conflicts of interest: none declared.

References

1 Murray C J L, Ortblad K F, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 1005–1070.
2 World Health Organization. Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases. Geneva, Switzerland: WHO, 2015.
3 Venkatesh K K, Swaminathan S, Andrews J R, Mayer K H. Tuberculosis and HIV co-infection: screening and treatment strategies. Drugs 2011; 71: 1133–1152.
4 Isaakidis P, Varghese B, Mansoor H, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLOS ONE 2012; 7: e40781.
5 World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland: WHO, 2015.
6 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. Geneva, Switzerland: WHO, 2015.
7 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. WHO/HTM/TB/2011.6. Geneva, Switzerland: WHO, 2011.
8 Ministry of Health and Social Services. National guidelines for the management of tuberculosis. 3rd ed. Windhoek, Namibia: MoHSS, 2012.
9 Ministry of Health and Social Services. National guidelines for antiretroviral therapy. 4th ed. Windhoek, Namibia: MoHSS, 2014.
10 Melnick J Z, Baum M, Thompson J R. Aminoglycoside-induced Fanconi's syndrome. Am J Kidney Dis 1994; 23: 118–122.
11 Fernandez-Fernandez B, Montoya-Ferrer A, Sanz A B, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat 2011; 2011: 354908.
12 Kenyon C, Wearne N, Burton R, Meintjes G. The risks of concurrent treatment with tenofovir and aminoglycosides in patients with HIV-associated tuberculosis. South Afr J HIV Med 2011; 12: 43–45.
13 Corbell C, Katjitae I, Mengistu A, et al. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. Pharmacoepidemiol Drug Saf 2012; 21: 407–414.
14 National Institute of Diabetes and Digestive and Kidney Diseases. Estimating glomerular filtration rate (GFR). Bethesda, MD, USA: NIDDK, 2015.
15 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; 48: 452–458.
16 Berman L B, Katz S. Kanamycin nephrotoxicity. Ann N Y Acad Sci 2006; 76: 149–156.
17 Mingeot-Leclercq M P, Tulkens P M. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother 1999; 43: 1003–1012.
18 Hall A M, Bass P, Unwin R J. Drug-induced renal Fanconi syndrome. QJM 2014; 107: 261–269.
19 Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis 2003; 36: 1070–1073.
20 Hall A M, Hendry B M, Nitsch D, Connolly J O. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis 2011; 57: 773–780.
21 Paller M S. Drug-induced nephropathies. Med Clin North Am 1990; 74: 909–917.
22 Hoitsma A J, Wetzels J F, Koene R A. Drug-induced nephrotoxicity. Aetiology, clinical features and management. Drug Saf 1991; 6: 131–147.
23 Ministry of Health and Social Services. National Guidelines for Antiretroviral Therapy. 3rd ed. Windhoek, Namibia: MoHSS, 2010.
24 Joseph K S, Mehrabadi A, Lisonkova S. Confounding by indication and related concepts. Curr Epidemiol Reports 2014; 1: 1–8.
25 Röling J, Schmid H, Fischereder M, Draenert R, Goebel F D. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. Clin Infect Dis 2006; 42: 1488–1495.
26 Kumar N, Perazella M A. Differentiating HIV-associated nephropathy from antiretroviral drug-induced nephropathy: a clinical challenge. Curr HIV/AIDS Rep 2014; 11: 202–211.
27 Gérard L, Chazallon C, Taburet A-M, Girard P-M, Aboulker J-P, Piketty C. Renal function in antiretroviral-experienced patients treated with tenofovir disoproxil fumarate associated with atazanavir/ritonavir. Antivir Ther 2007; 12: 31–39.
28 Antoniou T, Raboud J, Chirhin S, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. HIV Med 2005; 6: 284–290.

RÉSUMÉ

CONTEXTE : Comparer l'insuffisance rénale parmi les patients atteints de tuberculose multirésistante (TB-MDR) traitées par un protocole à base de kanamycine (KM) avec ceux traités concomitamment par tenofovir disoproxil fumarate (TDF) ou d'autres protocoles de traitement antirétroviral (ART) en Namibie.

SCHÉMA : Revue rétrospective des dossiers de traitement et des tests de laboratoire des patients mis sous traitement de TB-MDR (janvier–décembre 2014). Les taux estimés de filtration glomérulaire (eGFR) avant/après traitement ont été comparés avec l'analyse de variance. L'insuffisance rénale a été définie comme un eGFR de <60 ml/min/1,73 m^2. L'association entre utilisation de KM ou de TDF et d'insuffisance rénale a été évaluée avec les courbes Kaplan-Meier et l'analyse de risque proportionnel de Cox.

RÉSULTATS : L'eGFR moyen de départ a été similaire pour les trois groupes ($P = 0,24$), 139,3 ± 25,6 ml/min pour le groupe KM ($n = 68$), 131,1 ± 25,7 ml/min pour le groupe KM+TDF ($n = 44$) et 134,2 ± 34,4 ml/min pour le groupe KM+Autre médicament ($n = 23$). Après 8 mois, les valeurs avaient significativement décliné à 104,8 ± 37,5 ml/min ($P < 0,001$), 101,5 ± 38,3 ml/min ($P < 0,001$) et 111,5 ± 41,7 ml/min ($P = 0,01$) respectivement. Le co-traitement par KM+ART a été associé avec un risque élevé d'insuffisance rénale (risque relative [HR] 1,8 ; IC95% 0,7–4,1 ; $P = 0,20$ pour KM +TDF, HR 3,5 ; IC95% 1,4–8,2 ; $P = 0,005$ pour KM+Autres ART).

CONCLUSION : La fonction rénale a décliné à un taux similaire chez les patients TB-MDR traités par des protocoles basés sur la KM comparés aux patients concomitamment traités par ART basée sur TDF ou d'autres médicaments. Le risque d'insuffisance rénale a été plus élevé pour les patients sous ART.

RESUMEN

MARCO DE REFERENCIA: Comparar la aparición de insuficiencia renal en los pacientes con tuberculosis multirresistente (TB-MDR) tratados con un régimen basado en kanamicina (KM) y los pacientes que reciben de manera concomitante fumarato de disoproxilo de tenofovir (TDF) u otro régimen de tratamiento antirretrovírico (ART) en Namibia.

MÉTODO: Se llevó a cabo un análisis retrospectivo de los registros de tratamiento y las pruebas de laboratorio de los pacientes que iniciaron tratamiento por TB-MDR (de enero a diciembre del 2014). Las tasas de filtración glomerular estimadas (eGFR), antes y después del tratamiento, se compararon mediante el análisis de variancia bilateral. La insuficiencia renal se definió como una eGFR <60 ml/min/1,73 m^2. La asociación entre la utilización de KM o TDF y la insuficiencia renal se evaluó en diagramas de Kaplan-Meier y un modelo de riesgos proporcionales de Cox.

RESULTADOS: El promedio de la eGFR inicial en los tres grupos fue equivalente ($P = 0,24$), a saber: 139,3 ± 25,6 ml/min en el grupo que recibió KM ($n = 68$), 131,1 ± 25,7 ml/min en el grupo tratado con KM+TDF ($n = 44$) y 134,2 ± 34,4 ml/min en el grupo de KM+Otro ART ($n = 23$). Después de 8 meses, las cifras disminuyeron de manera significativa a 104,8 ± 37,5 ml/min ($P < 0,001$); 101,5 ± 38,3 ml/min ($P < 0,001$); y 111,5 ± 41,7 ml/min ($P = 0,01$), respectivamente. El tratamiento concomitante de KM+ART se asoció con un alto riesgo de aparición de insuficiencia renal (cociente de riesgos instantáneos [HR] 1,8; IC95% 0,7–4,1; $P = 0,20$ con KM+TDF y HR 3,5; IC95% 1,4–8,2; $P = 0,005$ con KM+Otro ART).

CONCLUSIÓN: Las tasas de disminución de la función renal fueron equivalentes en los pacientes con TB-MDR tratados con regímenes a base de KM, en comparación con los pacientes que recibieron de manera concomitante un ART con TDF u otro fármaco. El riesgo de insuficiencia renal fue mayor en los pacientes que recibían ART.