Original Research

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Effect of changing from first- to Second- Line Antiretroviral Therapy on Renal Function: A Retrospective Study based on data from a Single Health Facility in Namibia

Short Title: Effect of changing ARVs on renal function

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Abstract

Tenofovir disoproxil fumarate (TDF) and lopinavir/ritonavir (LPV/r) can cause renal impairment with this combination co-administered during second-line combination antiretroviral therapy (cART) potentially associated with greater risk of nephrotoxicity. Objective: Assess effects of second-line cART on renal function. Methods: Retrospective longitudinal study in patients receiving cART. Results: 71 patients received TDF, zidovudine or stavudine, each combined with 3TC/NVP or 3TC/EFV. Before second-line cART, 46.5% had abnormal kidney function. First-line cART had no relationship with calculated creatinine clearance (CrCl). During second-line cART, more males than females had abnormal renal function and more females experienced increases in CrCl. Calculated CrCl during second-line cART related strongly with CrCl during first-line cART; time spent on cART weak relationship with CrCl. Conclusion: Patients on first-line cART for several years without renal impairment may experience new onset impairment during cART. Patients with pre-existing renal impairment just before switching to second-line cART may experience a further decline.

Key words: Namibia, renal function, creatinine clearance, combination antiretroviral therapy, drug utilisation study

Introduction

Initiatives supporting the availability and accessibility of cART have significantly reduced morbidity and mortality of people infected with the HIV in resource limited settings [1]. Despite the positive impact on patient survival, antiretrovirals (ARVs) can cause adverse drug reactions (ADRs). Tenofovir Disoproxil Fumarate (TDF) is known to cause acute and chronic renal impairment [2]. Similarly, lopinavir /ritonavir (LPV/r) , is associated with renal ADRs [3, 4]. The preferred first-line cART regimen is TDF/lamivudine (3TC)/Nevirapine (NVP) or Efavirenz (EFV). At the time of writing this paper, LPV/r is the only PI available for second-line cART in the public sector in Namibia, and is co-administered with TDF, 3TC and AZT [5]. Since TDF and LPV/r are associated with nephrotoxicity, their co-administration poses a higher risk for renal impairment [6, 7]. It should be noted that the risk of renal impairment may be influenced by gender, because of the hormonal differences between males and females [8]. Namibia's 2010 and 2014 cART guidelines recommended the calculation of CrCl every

six months for all patients receiving TDF-containing cART. The calculated CrCl provides evidence on which TDF's dosing intervals are either prolonged or unchanged [9]. Since Namibia is an ethnically diverse nation, the Cockcroft-Gault (C-G) method is preferred because it does not grade the patients' CrCl based on ethnicity.

TDF undergoes renal elimination through a combination of glomerular filtration and active tubular secretion. The efflux of TDF from the tubular cells into the filtrate is mediated by Adenosine-5'-Triphosphate Binding Cassette (ABC) C4 and Multi-Drug Resistance Protein-4 (MRP-4) and MRP-7 [10]. By inhibition of the mitochondrial DNA-polymerase gamma, TDF impairs the functioning of energy dependent transporters [11,12]. Ritonavir (RTV) has a minimal effect on MRP-4. Hence, the effects of ritonavir seem not to increase renal exposure to TDF [13]. Nevertheless, the co-administration of TDF with RTV is associated with increased risk of renal impairment, and it is believed that the inhibition of the permeation glycoprotein – MRP-4 – by RTV results in increased exposure of TDF to the proximal tubular cells [14,15].

In a letter to the editors of JAIDS[1], Sorli *et al (*2008) said that the prevalence of kidney impairment amongst HIV infected patients receiving cART was 3.5% - 4.7%, and 15.5% among the black population [16]. Renal impairment is a cause for concern as it is an independent risk factor for cardiovascular disease (CVD) and is on the rise among HIV infected patients [17,18].

The co-administration of TDF and LPV/r and its effects on renal function in HIV-infected patients in Namibia has not been elucidated. As such, it was not known whether the risk of reduced renal function during the administration of cART was influenced by gender and/ or the length of time spent on second-line therapy. In this paper we present the outcomes, namely: decline or improvement, and give plausible explanations of these outcomes in HIV-infected patients who were receiving second-line cART to provide future guidance to decision makers.

Methods

Study design
This was a retrospective longitudinal study that employed a mixture of descriptive and analytical statistics.

Study setting
The study was implemented at the HIV clinic at the Katutura Intermediate Hospital (KIH).

Study population
A list of patients on second-line cART was generated from the electronic Dispensing Tool (EDT - The EDT is a computerised database that stores cART dispensing records for all patients receiving ART in the public sector in Namibia. The EDT provides the cART start date; all the medicine regimens the patient has received; any drug substitutions that were made, and the dates for any changes). Using key identifiers in the EDT, we accessed the patient care booklets (PCB) from which we extracted the data (PCBs are paper-based patient files which contain data on their medical, drug, and laboratory histories – including SeCr, and notes on progression of therapy). We acknowledge that changes in the frequency of clinic visits is one of the main interventions made to decongest HIV clinics, which happens in the majority of patients who are adherent to their ART and are responding well to the therapy.

Consistent with Namibia's ART guidelines, we calculated the CrCl. Similar to Bygrave *et al's* (2011) study on TDF and its effect on renal function, we categorised patients in their respective grades of renal function based on their CrCl as follows [9].

- **Definitions of renal function:** The categories of renal function into which the patients were classified are shown in Table 1.
- Any CrCl below 90ml/min was categorised as abnormal

[1] Journal of Acquired Immuno-Deficiency Syndrome

Table 1: Renal function categories, based on CG calculation

Grade	CrCl
I (Normal)	≥90
II (Mild)	60 – <90
III (Moderate)	30 – <60
IV (Severe)	<30

- Renal function was considered to have declined if the last CrCl during second-line cART was ≥25% less than the last CrCl during first-line therapy. In addition, when the SeCr was noted to have increased by ≥25%, during second-line cART, renal function was considered to have declined. A drop in CrCl from 20 - <25% was referred to as a reduction renal function
- Renal function was considered to have improved if the last CrCl during second-line treatment was ≥25% more than the last CrCl during first-line treatment. When the SeCr was noted to have decreased by ≥25%, during second-line treatment, coupled with a change of CrCl from abnormal to normal the renal function (even though the CrCl was <25%), this was considered to have improved

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Ethics

Anonymity of the patients and confidentiality with the data was assured. The study was approved first by the School of Pharmacy, Faculty of Health Sciences: University of Namibia, then by the Ministry of Health and Social Services (MoHSS), Namibia.

Statistical analysis

Frequency data was described and presented in tables. We used the Binomial Distribution test to assess whether the decline in renal function (that is, CrCl ≥25%) was statistically significant. We used McNemar's test to assess the changes in CrCl based on any reduction or increase ≥20ml/min. We used the Chi-square Test to determine if there was a difference between the number of males and females with abnormal renal function at the end of first-line cART, and during second-line treatment; and to assess the possible relationship between the first-line cART regimens and renal function. We used scatter plots and Spearman Correlation Co-efficient to visualise and explain the relationships between CrCl values; CrCl and patient age; and CrCl and time spent on second-line therapy. We used Spearman Correlation Co-efficient to explain the strength of relationships between the above mentioned variables. The confidence level was set at 95% and the statistical significance at a p-value of <0.05.

Findings

Frequency: Demographics and ART data

A total of 71 patients who were receiving second-line ART at KIH were included in the study. Female patients made up 57.7% of the population. The average age of the population at the time of switching from first-line to second-line cART was 42 years. The first-line ART regimen they received was TDF/3TC, AZT/3TC, and D4T/3TC each combined with either NVP or EFV. These patients spent an average of 5.2 years on first line cART. At the time of data collection, they had spent an average of 1.8 years on second-line cART (Table 2). All patients received TDF/3TC/AZT/LPV/r as the second-line regimen (Table 2), which was prescribed following evidence of immunologic, virologic, and clinical failure. Overall, Table 2 documents the total number of patients, the number per regimen, and the time period spent on first- and second- line ART by gender.

Table 2: Demographics and ART regimen data distributed by gender

	All	Females	Males
Total number of patients	71(100%)	41(57.7%)	30 (42.3%)
Average age of the patients (years)	42 (26 - 55)	41 (29-55)	43 (26-51)
First line ART Regimens			
TDF/3TC/EFV	18(25.4%)	11 (15.4%)	7 (10.0%)
TDF/3TC/NVP	25 (35.2%)	13 (18.3%)	12 (16.9%)
TDF/FTC/NVP	1 (1.4%)	1 (1.4%)	-
AZT/3TC/EFV	2 (2.8%)	1 (1.4%)	1 (1.4%)
AZT/3TC/NVP	14 (19.7%)	9 (12.7%)	5 (7.0%)
D4T/3TC/EFV	5 (7.0%)	1 (1.4%)	4 (5.6%)
D4T/3TC/NVP	6 (8.5%)	5 (7.0%)	1 (1.4%)
Second line ART Regimen			
TDF/3TC/AZT/LPV-r	71	41	30
Mean years on 1st line ART (range)	5.2 (1.2 - 10)	5.2 (1.2 - 9.9)	5.3 (1.3 - 10)
Mean years on 2nd line ART (ranget)	1.8 (0.7 - 2.6)	1.8(0.7 - 2.6)	1.7 (0.7 - 2.6)

Findings related to kidney function

SeCr tests

At the time of data collection, the patients had undergone two to five SeCr tests (Table 3).

Table 3: Number of SeCr results per-patient and outcomes on SeCr and CrCl

Period	Number of	
	SeCr tests per patient	Patients
Before and after switching to second-line cART	2	20 (28.2%)
	3	28 (39.4%)
	4	18 (25.4%)
	5	5 (7.0%)

CrCl results before second-line ART

Before initiation of second-line ART, almost half (46.5%, n=33) of the patients had abnormal renal function (that is <90ml/ min). Females and males accounted for 25.4% and 21.1%, respectively (Table 4). Overall, Table 4 documents the total number (percentage) of patients with normal kidney function at the end of first-line cART, which was slightly higher than the number with abnormal renal function. There was no statistically significant difference between females and males in the numbers of patients with abnormal renal function (p=0.61), (Table 4).

Table 4: Grades of renal function at the end of first-line ART

Grade of Renal Function	Number of Patients		
	All	Female	Male
Grade I (≥90ml/min)	38(53.5%)	23(32.4%)	15(21.1%)
Grade II (60 – <90ml/min)	32 (45.1%)	18 (25.4%)	14 (19.7%)
Grade III (30 – <60 ml/min)	1(1.4%)	_	1(1.4%)
Grade IV (<30 ml/min)	_	_	_

CrCl results during second-line ART

During second-line cART, the proportion of patients with abnormal renal function was not different from that during first line cART (46.5%, n=33). However, there were more males than females with abnormal renal function (p=0.01) (Table 5). The numbers (percentages) of patients who experienced decline, reduction, or improvement in CrCl and SeCr are shown in tables 6a (Tables 6b and 6c are extracts from table 6a). Overall, eight of the patients with ≥25% decline in CrCl also moved from grade I to grade II of the renal function grading system (Table 6). Four experienced a worsening of grade II. Of the patients who experienced a decline in SeCr ≥25ml/min, two had a change from abnormal renal function (78 and 79ml/min) to normal renal function (96ml/min and 95ml/min, respectively). Four of them had normal renal function.

Based on the binomial distribution test, a significant decline (≥25%) in CrCl, as opposed to improvement (≥25% reduction in SeCr coupled with a change from abnormal to normal CrCl), was observed (p = 0.000). Similarly, an analysis by McNemar's test, based on the fact that CrCl dropped by ≥25% in 12 patients and none had an increment in CrCl ≥25%, we found that there was a significant change in the number of patients who changed from normal to abnormal renal function (p =0.000).

Table 5: Grades of renal function during second line ART

Grade of Renal Function	Number of Patients		
	All	Female	Male
Grade I (≥90ml/min)	38(53.5%)	27(38.0%)	11(15.5%)
Grade II (60 – <90ml/min)	31(43.7%)	13(18.3%)	18(25.4%)
Grade III (30 - <60 ml/min)	2(2.8%)	1(1.4%)	1(1.4%)
Grade IV (– <30 ml/min)	_	_	_

Table 6a: Numbers of patients with changes in renal function based on CrCl and SeCr

	Number (%) of Patients		
	CrCl	SeCr	
Percentage reduction in CrCl			Percentage increase in SeCr
≥25%	12 (16.9%)	3 (4.2%)	≥25%
10 - <20%	23 (32.4%)	11 (15.5%)	10 - <20%
<10%	13 (18.3%)	22 (31.0%)	<10%
Sub-totals	*59 (83.1%)*	*39(54.9%)*	
Percentage increase in CrCl			Percentage decrease in SeCr
≥25%	-	6 (8.5%)	≥25%
20 - <25%	3 (4.2%)	3 (4.2%)	20 - <25%
10 - <20%	3 (4.2%)	9 (12.7%)	10 - <20%
<10%	6 (8.5%)	14 (19.7%)	<10%
Sub-totals	*12 (16.9%)*	*32(45.1%)*	

Table 6b: Gender-based breakdown of CrCl outcomes of renal function during second-line ART

Renal function status	Number of Patients		
	All	Females	Males
Decline in CrCl ≥25%	12 (16.9%)	4 (5.6%)	8 (11.3%)
Decline or improvement in CrCl <25%	59 (83.1%)	37 (52.1%)	22 (30.9%)
Improvement in CrCl ≥25%	-	-	-

Table 6c: Gender-based breakdown of SeCr outcomes of renal function during second-line ART

Renal function status	Number of Patients		
	All	Females	Males
Increase in SeCr ≥25%	3 (4.2%)	1 (1.4%)	2 (2.8%)
Increase or decrease in SeCr <25%	62 (87.3%)	36 (50.7%)	26 (36.6%)
Decrease in SeCr ≥25%	6 (8.5%)	4 (5.6%)	2 (2.8%)

Effect of first-line ART regimens on CrCl

There was no difference between TDF-based and TDF-sparing first-line ART regimen, on the CrCl (95% CI: 102 [94-111] vs. 95 [87-102] ml/min; p=0.78). Furthermore, we observed that the type of first-line (TDF-based vs. TDF-sparing) regimen did not influence the CrCl during second-line ART (95%CI: 105 [96-114] vs. 96 [87-104] ml/min; P=0.90).

Relationships between variables

- There was a strong positive relationship between the CrCl before second line therapy and the CrCl during second line cART (r=0.8; p=0.000)
- There was a mild-strength negative relationship between patient age and CrCl during first line cART (r=0.3)
- During second-line cART, the relationship was similar to that observed during first-line ART; however, it was slightly stronger (r=0.4)

- There was no covariance between the time spent on cART and CrCl during second- line cART treatment (r=0.1, p>0.05),

Overall, CrCl did not co-vary with time spent on first line or second line cART (Figures 1 and 2).

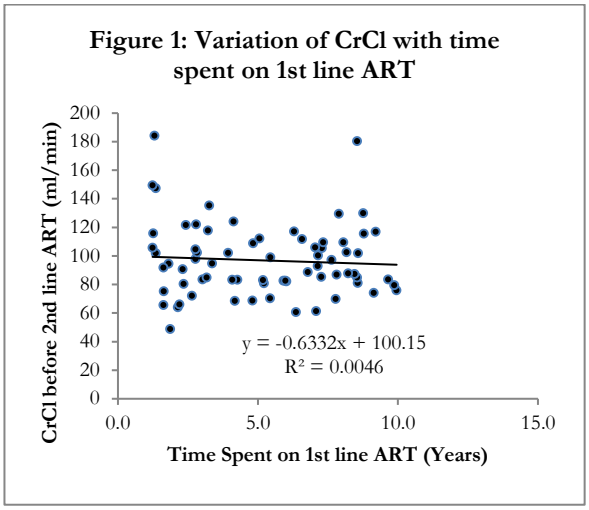

Figure 1: Variation of CrCl with time spent on 1st line ART

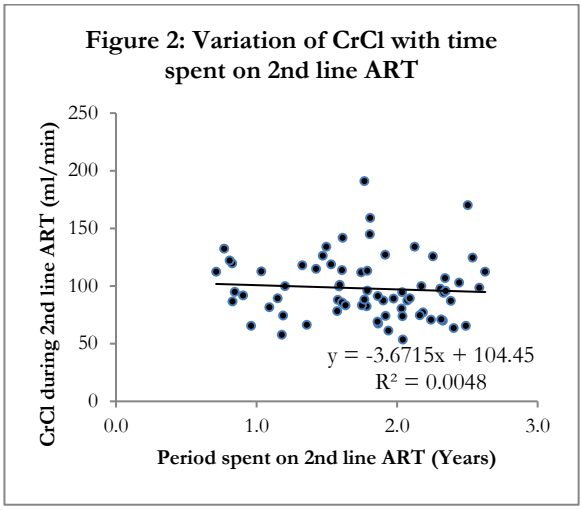

Figure 2: Variation of CrCl with time spent on 2nd line ART

Discussion

Renal Function during First-line cART

In our study, the proportion of patients with renal impairment during first-line treatment was large, but this observation was not interpretable as an increased incidence of ARV-induced renal disease for a number of reasons. Firstly, the patients had experienced treatment failure, and were therefore not representative of the population of patients normally receiving first-line treatment. Secondly, some patients may have experienced HIV-associated renal impairment as their viral load was high. Thirdly, pre-existing renal impairment at the time of cART initiation could have been a contributing factor for renal impairment before switching to second-line treatment. Lastly, because of lack of data concerning co-morbidities, other potential causes of renal impairment could not be ruled out.

Decreased Renal Function during Second-line cART

Some patients, who had normal renal function before switching, experienced new onset decline in CrCl. Others seemed to experience a further reduction in CrCl. A large multinational cohort study – The D:A:D[2] Study – had shown that renal impairment progresses with increasing time of exposure to TDF [19]. However, due to the great inter-patient variability in this study, the length of exposure to TDF-containing cART was weakly associated with the decline in CrCl (r=0.1). Since the population we studied was small and different in structure to that of the D:A:D study, we do not believe our findings are different to those of the D:A:D study. Advancing age is a known risk factor for reduced renal function [20]. Our findings are in agreement with this physiological norm, although the strength of the relationship between age and CrCl during second-line cART was moderate (r=0.4). A low CrCl before initiation of cART is another risk factor for further decline in renal function, especially if patients are exposed to nephrotoxic agents [21]. For that reason, the Namibian cART guidelines recommend the avoidance of TDF in patients with a CrCl below <60ml/min [5,22]. In a study by Gallant and Moore (2009), TDF-based first-line treatments were shown to cause an initial decline in renal function which lasted around 180 days [23]. A similar result was shown in a study by Miguel et al. (2008) [24]. As such, patients with a CrCl <60ml/min may experience a clinically significant regression in their renal function necessitating TDF's withdrawal. The perfect positive co-variation (r=0.9) of the baseline with

[2] Data Collection on Adverse Events of Anti-HIV Drugs

the outcome CrCl observed in this study is in agreement with this rule. However, the few cases of new-onset declines in, and cases of normalisation of renal function, are diversions to this rule.

This information calls for further observation and assessment of the safety of recommended second-line treatments in Namibia. On the other hand, the observed decline in renal function may have stabilised at stage II of renal function, meaning that further declines are not expected. The pharmacodynamic interaction between TDF and LPV/r partly explains the pathological basis of new-onset and further declines in renal function.

Improvement of renal function /CrCl

Some patients who had abnormal renal function at the end of first line therapy experienced improvement. Some experienced a rise in CrCl <25%. The patients whose renal function improved (CrCl increased by ≥25%), and those whose CrCl increased by 20 - <25% -, had received first-line treatment for a mean period of 3.2 years. Consequently, ARV-associated nephropathy is worth suspecting. However, the increment in CrCl that occurred during the administration of two nephrotoxic agents – TDF and LPV/r - leaves room for one possible explanation, i.e. the renal impairment that occurred in this particular group of patients was HIV-associated due to treatment failure.

Renal impairment in the setting of treatment failure can be judged to be induced by TDF, but this may not always be the case. Consequently, detection of renal impairment in patients receiving TDF-containing cART can falsely increase pharmacovigilance-based reports of TDF-associated renal impairment, and the time of occurrence and the other clinical events at that particular time need to be taken into account before TDF is assumed to be the cause of the observed renal impairment. One key observation is that the majority of patients who were observed to have experienced renal impairment during second-line cART (n=11) had a CrCl >50ml/min, the threshold below which TDF's dosage is advised [25].

Limitations

Our study had a number of limitations. Firstly, we categorised some patients' renal function on the basis of one or two SeCr results, yet SeCr levels are known to vary in the same patient due to factors other than renal impairment, e.g., the factors associated with an increase in SeCr include an increase in muscle mass, some co-administered drugs such as trimethoprim and cimetidine, and the ingestion of cooked meats. Factors associated with a decrease in SeCr include muscle wasting, amputation, and a vegetarian diet [26]. Consequently, misclassification of renal function could not be ruled out from our findings. Nevertheless, the majority of patients we observed to have experienced a decline in their renal function (10 out of 12) had more than two SeCr tests during second-line treatment: five had three, four had four, and one had five tests, and these tests were carried out between 0.8 – 2.2 years - these patients had spent a mean of 1.7 (1.3-2.2) years on second line cART. The Namibia cART guidelines that were in force during this study recommended that patients' renal function should be assessed every six months. Based on the number of SeCr tests carried out for these patients, the Namibia cART guidelines were generally complied with. However in light of the fact that there were unmeasured confounders, we advise that there is caution around these findings. The same caution, for the same reasons, should be exercised when interpreting the findings for patients who seemed to experience an increase in CrCl. Secondly, our study only had a relatively small number of patients. This was due to the fact that our facility only had relatively few patients receiving second-line treatment. Thirdly, we acknowledge that we did not abstract data on renal function pre- first-line, and this missing data led to speculations about the findings at the end of first-line, even though these speculations were clinically sound. Fourthly, there was variation in the length of time between the last measurement of SeCr and the switch date. It could have been that the CrCl just before switching was lower or even higher than what we considered as baseline. However, the fact that renal function was observed to improve during second-line treatment appears to addresses the concern for low CrCl, but for high CrCl patients this would mean no change in renal function. Overall though we believe our findings are valid and provide direction to the authorities in Namibia.

Conclusion

Exposure to second-line ART is likely to result in two major outcomes with respect to renal function, namely: decline or improvement. Our findings showed that patients who have received first-line

regimens for several years without renal impairment may experience new onset renal impairment during second-line treatments containing TDF, 3TC, AZT and LPV/r. Our findings also showed that patients who were switched to second-line cART with pre-existing renal impairment may experience a further decline in renal function. For these two categories of patients – new onset and worsening renal impairment - the decline in renal function was likely drug induced. To identify the causative agent is challenging as the renal impairment may be caused by TDF alone or a combination of TDF and LPV/r, or RTV alone.

Renal impairment that co-occurs with failure of first-line treatment may be HIV- rather than ARV - related. Our study also showed that the outcome of renal function during second-line treatment was instrumental in determining whether the former or the latter was the cause of renal impairment during first-line therapy. If the cause was HIV-related, resolution of renal impairment would occur following the use of potent second-line regimens. When a further decline in renal function occurs during the use of potent second-line regimens, the suspicion for it being ARV-induced is stronger, whether or not TDF was part of the first-line regimen.

Our findings showed that male patients were more at risk of renal impairment than female patients when exposed to second-line regimens containing TDF and LPV/r. However, notice should be given to the small sample size and to the relatively short time spent on second-line regimens among our patient population.

Pre- second-line CrCl could be a predictor of the CrCl during second-line treatments; however, new onset renal impairment and improvements in renal function cannot be ruled out. Careful follow up with renal function tests for all patients receiving second-line treatment is clinically valuable. We could not conclude though on the possible future outcomes of renal function for those patients whose renal function was normal before and during second-line cART.

Since renal impairment increases a patient's risk of CVD, further studies need to be undertaken to estimate the prevalence of renal impairment during first- and second- line cART in Namibia. This includes patients of both sexes given the low numbers of female patients in most studies amongst Western populations. The estimated prevalence will be useful for justification of possible interventions such as the replacement of TDF with TAF in resource limited settings, as the latter may be safer, but possibly more costly. Such information could also be used for the design of measures to protect patients against CVD.

Key Messages

- Patients who received TDF-containing cART during first-line treatment and do not develop renal impairment, may develop renal impairment during second-line cART. Continued monitoring of renal function is critical.
- Concurrent renal impairment with cART failure could result in over reporting of TDF-related renal reactions, giving a wrong perception of TDF's safety. Consequently, it is advisable for health care workers to report the incident as TDF-related only if renal impairment persists or declines further during the use of a potent second-line regimens.
- The presence of renal impairment during the use of TDF/3TC/EFV or NVP, does not contraindicate the prescription of TDF/3TC/AZT/LPV/r, but the patients' renal function should be monitored regularly
- HIV infected men are more susceptible to renal impairment associated with TDF/3TC/AZT/LPV/r than women.
- A larger and robust study is required to assess renal function in first- and second- line patient groups

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Reference

[1] Lawn SD, AD Harries , R Wood, "Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings," *Curr Opinion HIV AIDS,* pp. Jan;5(1):18-26.doi:10.1097/COH.0b013e328333850f., 2010.

[2] Fernandez-Fernandez B, Montoya-Ferrer, AB Sanz, MD Sanchez-Nino, CM Izquierdo, J Poveda, V Sainz-Prestel, N Ortiz-Martin, A Parra-Rodriguez, R Selgas, M Ruiz-Ortega, J Egido, and A Ortiz, "Tenofovir Nephrotoxicity: 2011 Update," *AIDS Research and Treatment,* vol. Volume 2011 (2011), no. Article ID 354908, 11 pages, p. 11, 2011.

[3] Shafi T, MJ Choi, LC Racussen, LA Spacek, C Berry, M Atta, and DM Fine, "Ritonavir-Induced acute kidney injury: kidney biopsy findings and review of literature," *Clin Nephrol,* pp. February; 75(01): 60-64, 2011.

[4] M. Boffito, From Concept to Care: Pharmacokinetic Boosting of Protease Inhibitiors, London: Physicians Research Network, Inc(R), New Yor City., 2004.

[5] Ministry of Health and Social Services, Namibia, in *National Guidelines for Antiretroviral Therapy*, Windhoek, 2015, p. 13.

[6] Ketan K Patel, Atul K Patel, Jagdish K Patel, "Tenofovir-associated Renal Dysfunction in Clinical Practice: An Observational Cohort from Wester India," *Indian J Sex Transm Dis,* vol. 31, no. 1, pp. 30-34, 2010 Jan-Jun.

[7] Ying Cao, Yang Han, Jing Xie, Qu Cui, Lixia Zhang, Yijia Li, Xiaojing Song, Ting Zhu, Taisheng Li, "Impact of a Tenofovira Disoproxil Fumarate plus Ritonavir-boosted Protease Inhibitor-based Regimen on Renal Function in HIV-infected Individuals: A prospective, Multicentre Study," *BMC Infectious Diseases,* vol. 13, no. 301, 2013.

[8] I Sabolic, AR Asif, WE Budach, C Wanke, A Bahn, G Burckhardt, "Gender Differences in Kidney Function," *Pflugers Arch,* vol. 3, no. 455, pp. 397-429, 2007.

[9] Ministry of Health and Socia Sevices, Namibia, in *National Guidelines for Antiretroviral Therapy, Fourth Edition*, Windhoek, 2014, p. 17.

[10] Adrian S Ray, Toma Cihlar, Kelly L Robinson, Leah Tong, Jennifer E Vela, Michael D Fuller, Lani M Wieman, Eugen J Eisenberg, and Gerry R Rhodes, "Mechanis of Active Renal Tubular Efflux of Tenofovir," *Antimicrobial Agents and Chemotherapy,* vol. 50, no. 10, pp. 3297 - 3304 doi:10.1128/AAC00251 - 06, 2006.

[11] Iwen F Grigby, "Tenofovir-associated bone density loss," *Therapeutics and Clinical Risk Managment,* 2009.

[12] Darren M Moss, Megan Neary, and Andrew Owen, "The Role of Drug Transporters in the Kidney: Lessons from Tenofovir," *Frontiers in Pharmacology,* vol. 5, no. 248, 2014.

[13] Brian P Kearney, Anita Mathias, Angelique Mittan, John Sayre, Ramin Ebrahim, Andrew K Cheng, "Pharmacokinetics and Safety of Tenofovir Disoproxil Fumarate on Coadministration with Lopinavir/Rtionavir," *J Acquir Immune Defic Syndr. ,* vol. 3, no. 43, pp. 278 - 283, 2006.

[14] Kiser JJ, Carten ML, Aquilante CL, Anderson PL, Wolfe P, King TM, Delahunty T, Bushman LR, Fletcher CV, "The Effect of Lopinavir/ritonavir on the Renal Clearance of Tenofovir," *Clin Pharmacol Ther,* vol. 2, no. 83, pp. 265 - 72, 2008 Feb;83(2):.

[15] Jean C. Yombi; Anton Pozniak; Marta Boffito; Rachael Jones; Saye Khoo; Jeremy Levy; Frank A. Post, "Antiretroviral and the Kidneys in Current Clinical Practice," *AIDS,* vol. 5, no. 28, pp. 621 - 632, 2014.

[16] Sorli Maria L, Guelar Ana, Montero Milagro, Gonzalez Alicia, Rodriguez Eval, Knobel Hernando, "Chronic Kidney Disease Prevalence and Risk Factors Among HIV-Infected Patients," *Journal of Acquired Immune Defficiency Syndromes,* vol. 48, no. 4, pp. 506 - 508, 2008.

[17] Mark J Sarnak, Andrew S Levey, Anto C Shoolwerth, Josef Coresh, Bruce Culleton, L. Lee Hamm, Peter A McCullough, Betram L Kasiske, Ellie Kelepouris, Michael J. Klag, Patrick Parfrey, Marc Pfeffer, Leopold Raij, David J Spinosa, Peter W Wilson, "Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statment From the American Heart Association Counceils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention," *Circulation, Journal of The American Heart Association,* no. 108, pp. 2154 - 2169, 2003.

[18] Dererk M. Fine and Joel E. Gallant, "Nephrotoxicity of Antiretroviral Agents: Is the List Getting Longer?," *The Journal of Infectious Diseases,* 2013.

[19] Amanda Mocroft, Jens D Lundgren, Michael Ross, Christoph A Fux, Peter Reiss, Oliver Morane, Phillipe Morlat, Antonella d'Arminio Monforte, Ole kirk, Lene Ryom, "Cumulative and Current Exposure to Potentially Nephrotoxic Antiretrovirals and Development of Chronic Kidney Disease in HIV-postive Individuals with a Normal Baseline Estimated Glomerular Filtration rate: A Prospective Internation Cohort Study," *The Lancet HIV,* vol. 3, no. 1, pp. e23 - e32, 2015.

[20] Jessica R Weinstein and Sharon Anderson, "The Aging Kidney: Physiological Changes," *Adv Chronic Kidney Dis,* vol. 17, no. 4, pp. 302 - 307. doi:10.1053/j.ackd.2010.05.002, 2010.

[21] Lloyd Mulenga, Patrick Musonda, Albert Mwango, Michael J Vinikoor, Mary-Ann Davies, Aggrey Mweemba, Alexandra Calmy, Jeffrey S. Stringer, Olivia Keiser, Benjamin H. Chi, and Gilles Wandeler, "Effect of Baseline Renal Function on Tenofovir-Containing Antiretroviral Therapy Outcomes in Zambia," *Clinical Infectious Diseases,* 2014.

[22] Department: Health, Republic of South Africa, "The South African Antiretroviral Treatment Guidelines," pp. 11 - 13, 2013.

[23] Joel E Gallant, and Moore RD, "Renal function with use of a tenofovir-containing initial antiretroviral regimen.," *AIDS,* vol. Sep 24;23, no. (15), pp. 1971-5. doi:

10.1097/QAD.0b013e32832c96e9., 2009.

[24] Miguel Goicoechea, Shanshan Liu, Brookie Best, Shelly Sun, Sonia Jain, Carol Kemper, Mallory Witt, Catherine Diamond, Richard Haubrich, Stan Louie, and the California Collaborative Treatment Group 578, "Greater Tenofovir-Associated Renal Function Decline with Protease Inhibitor-Based versus Nonnucleoside Reverse-Transcriptase Inhibitor-Based Therapy," *J Infect Dis.,* vol. 197, no. (1), pp. 102 - 108, 2008.

[25] I. Gilead Sciences, Tenofovir Disoproxil Fumarate Prescribing Information, Foster City, CA, 2013.

[26] Martin E. Lascano and Emilio D. Poggio, "Kidney Function Assessment by Creatinine Based Estimation Equations," 2010.