

# Increased serum creatinine in patients taking tenofovir in combination with dolutegravir: queries to the National HIV and TB Health Care Worker Hotline in South Africa



Gayle Tatz<sup>1</sup>, Briony Chisholm<sup>2</sup>, Annoesjka Swart<sup>2</sup>, Anri Uys<sup>2</sup>, Karen Cohen<sup>1</sup>

<sup>1</sup>Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

<sup>2</sup>Medicines Information Centre, Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa

## BACKGROUND

- The National HIV and TB Health Care Worker Hotline in South Africa provides advice on the management of adverse drug events (ADEs).
- In December 2019, dolutegravir was included in South African antiretroviral therapy (ART) guidelines in preferred first and second line regimens.
- Dolutegravir decreases creatinine clearance due to renal transporter inhibition but is not nephrotoxic. The magnitude of this change is variable with a median decrease of 16%.<sup>1</sup>
- Changes in serum creatinine secondary to dolutegravir's effect on renal transporters stabilise within four weeks of initiating dolutegravir.<sup>1</sup>
- Tenofovir disoproxil fumarate (tenofovir) may cause renal injury.<sup>2,3</sup>
- South African National ART guidelines advise that tenofovir-containing regimens should not be selected for patients with a baseline estimated Glomerular Filtration Rate (eGFR) of <50 mL/min/1.73m<sup>2</sup> and that tenofovir should be substituted for another non-nucleoside reverse transcriptase inhibitor when eGFR < 50 mL/min/1.73m<sup>2</sup>.<sup>2,4</sup>
- Timeous diagnosis of tenofovir-induced renal injury is important in settings with limited access to dialysis. However, drug-substitution due to renal transporter effects of dolutegravir without renal injury may result in increased pill burden.

## OBJECTIVE

- To describe renal ADEs in patients taking tenofovir in combination with dolutegravir reported to the National HIV and TB Health Care Worker Hotline.

## METHODS

- All Hotline queries were prospectively captured in an Access database.
- For this case series, we included all renal ADEs in patients on tenofovir in combination with dolutegravir received between 1 January 2020 and 28 February 2021.
- We collected follow up information on renal ADE queries where possible.
- Callers reported serum creatinine results and/or eGFR results. In queries where only a serum creatinine was reported, the eGFR was calculated using the CKD-EPI equation<sup>6</sup>.

## RESULTS

- The Hotline received 819 queries about treatment-related ADEs in patients with HIV and/or TB during the study period, of which 29 concerned renal ADEs in patients on tenofovir in combination with dolutegravir.
- Percentage increase in creatinine after introduction of tenofovir with dolutegravir ranged from 12% to 111%.
- eGFR was <50 mL/min/1.73m<sup>2</sup> in 16 of 29 patients
- Nine queries involved adult patients who initiated tenofovir plus lamivudine plus dolutegravir (TLD) as their first antiretroviral therapy regimen**
  - In 8/9 patients, an eGFR of <50 mL/min/1.73m<sup>2</sup> was reported post initiation of TLD
    - In 2/8 eGFR was <50 mL/min/1.73m<sup>2</sup> before TLD initiation, which had been initiated inappropriately. In one, tenofovir had already been substituted with abacavir. In the other, the Hotline advised to substitute tenofovir with abacavir.
    - In 1/8, first line antituberculosis treatment had been commenced together with TLD. All medications were stopped prior to the query. The Hotline assessed both tenofovir and rifampicin as potential causes of renal dysfunction and advised that neither be recommended.
    - One switched from TLD to abacavir, lamivudine and efavirenz prior to making the query. The Hotline's advice was to continue this regimen
    - The remaining four were advised to substitute tenofovir with abacavir
  - The remaining patient had an eGFR of 59 mL/min/1.73m<sup>2</sup> post initiation of TLD. The Hotline advised substituting tenofovir with abacavir
- Twenty queries involved patients who had switched from another ART regimen to TLD.**
- 16/20 were adults switched from a tenofovir-containing regimen (tenofovir plus emtricitabine plus efavirenz in 14/16) to TLD. (See Table 1)
- 4/20 were adolescents switched to TLD from other antiretroviral regimens
  - All four adolescents had normal baseline renal function and eGFR > 90 mL/min/1.73m<sup>2</sup> after switching to TLD, and the Hotline recommended continuing TLD.
    - In one, tenofovir was substituted with abacavir despite a preserved eGFR and advice from the Hotline not to switch. The clinician making the query remained concerned about the 111% increase in creatinine.
  - In all four adolescents, creatinine had stabilised on follow up.
- Regimen switches resulted in increased pill-burden in 21 of 24 patients (87.5%).

## LIMITATIONS

- This is a case series identified from queries made to The National HIV & TB Health Care Worker Hotline. There is no denominator data and therefore we cannot determine the prevalence of renal ADEs in patients on tenofovir with dolutegravir.

## CONCLUSIONS

- We observed a wide range in proportional change in creatinine after commencing dolutegravir with tenofovir, in keeping with previous studies<sup>1,5</sup>.
- Prescribers were concerned about changes in creatinine, despite eGFR remaining above the threshold at which the South African National guidelines recommend stopping tenofovir. In one case, the clinician switched from tenofovir to abacavir at an eGFR >90 mL/min/1.73m<sup>2</sup> against hotline advice.
- Unnecessary switches in antiretroviral treatment should be avoided. Switches may increase pill burden and impact on adherence.
- Health care workers in resource limited settings require training and support regarding investigation and management of serum creatinine increases in patients receiving tenofovir with dolutegravir.

**Table 1. Adult patients switched from a tenofovir-containing antiretroviral therapy regimen to tenofovir plus lamivudine plus dolutegravir.**

eGFR at time of query (mL/min/1.73m <sup>2</sup> )	Number of cases	SCr/eGFR prior to switch	ART regimen at time of query	Advice given by hotline	Follow up information
<50	8	1 abnormal, 7 in normal range	ABC plus 3TC plus DTG (2 cases) TDF plus 3TC plus DTG (6 cases)	Continue ABC (2) Replace TDF with ABC (6)	None (8)
50-60	3	All in normal range	ABC plus 3TC plus DTG (2 cases, with follow up) TDF plus 3TC plus DTG (1 case)	Continue ABC (2) Switch from TLD to ABC plus 3TC plus EFV(1),	Renal dysfunction stabilised (1) SCr increase from 110-125 µmol/L (1), No follow up (1)
60-90	4	All in normal range	ABC plus 3TC plus DTG (2 cases) TDF plus 3TC plus DTG (2 cases)	Continue ABC (2) Replace TDF with ABC (1) Stay on current regimen(1)	None (8)
>90	1	All in normal range	Clinician stopped ART due to suspected DTG-induced liver injury and increase in SCr from 61 to 102 µmol/L	Recommence antiretroviral therapy: ABC plus 3TC plus EFV	Renal dysfunction stabilised

Abbreviations: ART antiretroviral therapy; eGFR estimated Glomerular Filtration Rate; SCr serum creatinine; TDF tenofovir disoproxil fumarate; ABC abacavir; 3TC lamivudine; EFV efavirenz

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