Clinical Outcomes and Renal Safety in HIV/AIDS Patients on Tenofovir-containing Regimens in Lesotho

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Abstract: Although TDF use has been associated with acceptable safety, reports of rare manifestation of renal disease in HAART regimens that include TDF have been documented. The study was conducted at Paballong HIV/AIDS care centre in Berea, Lesotho. The aim of the study was to evaluate clinical outcomes and renal safety in HIV/AIDS patients taking TDF-containing HAART regimens. Descriptive, observational, longitudinal retrospective design was followed on 255 adults on TDF-containing HAART regimens at the study area; from October 2015 to March 2016. Data captured on a data collection tool included baseline, follow-up and end-line characteristics of clinical outcomes and renal safety. Patients gained an estimated body weight of to 0.10 kg from baseline (p < 0.05) at any age. Females were on average 2.49 kg heavier than males (p < 0.05). The CD4 cell count results estimated a daily increase of 0.20 cells/mm3 at any age. The mean CD4 cell count of female patients was 69.13 cells/mm3 higher than for males (p = 0.02). The eGFR results contended that sex, age and body weight are risk factors to developing renal insufficiency. The eGFR declined by 0.78 ml/min/1.73m2 over the treatment duration at any age of treatment initiation (p < 0.05), while the average eGFR for females was lower (13.05 ml/min) (p < 0.05). Clinical outcomes manifesting by weight gain and CD4 cell count elevation improve at any age and better in females. The renal function is progressively deteriorated at any age and worsened in females.

Keywords: Tenofovir, Clinical Outcomes, Renal Safety, Longitudinal Study, Paballong HIV/AIDS Care Centre

1. Introduction

1.1. Social Value

Tenofovir inclusion in highly active antiretroviral therapy regimens in the treatment of Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) has clinically shown to have an excellent efficacy and safety outcomes when compared with HAART regimens containing other first-line antiretroviral drugs, such as abacavir (ABC), stavudine (d4T) and zidovudine (AZT) [1, 2]. Although TDF use has been associated with acceptable safety, several studies have reported a rare manifestation of renal disease in HAART regimens that include TDF [3-8]. The antiretroviral therapy programmes have been scaled up significantly in the sub-Saharan Africa over the past decade, although there are still some challenges. United Nations Programme on HIV/AIDS (UNAIDS) witnessed this with findings by revealing 68% of people living with HIV infection in sub-Saharan Africa having access to antiretroviral treatment under the WHO 2010 guidelines (those with a baseline CD4 cell count of ≤350 cells/mm3) [9]. As of March 2015, 15 million people living with HIV infection worldwide were receiving antiretroviral treatment (including 823 000 children) [10]. This is representing 41% of those people in need of antiretroviral therapy. Of these 15 million people, 13.5 million patients were from low- and middle-income countries [10]. There is greater success for
access to antiretroviral therapy in low- and middle-income countries. The scaling-up of access to treatment is in the hearts of new global treatment targets for the year 2020 since the aim is to end the AIDS epidemic as a public health threat by the year 2030 [11].

The use of NRTIs/NtRTIs is associated generally with mitochondrial toxicities namely lactic acidosis, hepatic steatosis, lipodystrophy, pancreatitis and peripheral neuropathy; with the descending order of mitochondrial affinities: d4T, 3TC, AZT, ABC and TDF. Despite the fact that antiretroviral therapy decreases the susceptibility to developing chronic kidney disease coupled with CD4 cell recovery and viral suppression, some initial regimens including TDF increase the risk of developing renal toxicity [12-13].

1.2. Scientific Value

The antiretroviral regimens for initiation adopted by most national treatment programmes in most resource-limited settings included two NRTI/NtRTI and one NNRTI. The four TDF-containing HAART regimen combination derived from antiretroviral drugs have saved hundreds of thousands of lives and provided hope to millions of others. The regimens are TDF/3TC/NVP, TDF/FTC/NVP, TDF/3TC/EFV and TDF/FTC/EFV. TDF/3TC/EFV is safe and highly effective as a first-line non-nucleoside reverse-transcriptase inhibitor (NNRTI) regimen [14]. According to Louie et al. TDF is more potent and less toxic than AZT and d4T, with the median decline in plasma viral load in subjects receiving TDF, AZT or d4T mono-therapy at 1.4 log10, 0.5 log10, and 0.5 log10, respectively [15].

In a randomised, open-label non-inferiority trial, Pozniak et al. enrolled 517 antiretroviral-naïve, HIV-infected patients to receive either TDF/FTC/EFV or AZT/3TC/EFV [16]. Through the 96th week of treatment, more patients who received TDF/FTC significantly achieved and maintained a plasma viral level of < 400 copies/ml (75% versus 62%). The TDF/FTC group also demonstrated a significantly greater increase in CD4 cell counts (270 versus 237 cells/mm³, p = 0.036). Moreover, Arribas et al. conducted a long-term follow-up of the study for over 144 weeks in which TDF/FTC-based regimen confirmed the superior ability over the AZT/FTC-based regimen to suppress viral load without causing the lipodystrophy (seen with AZT/3TC-containing regimens) and with less effect on lipids [17]. Therapy with TDF is a strongly effective treatment option for achieving virologic response irrespective of treatment experience, combination therapy containing TDF and resistance to antiretroviral drugs [18].

The renal proximal tubule is the major site for TDF toxicit because this is the site at the neapher where the drug is excreted by secretion [19]. Hagos and Wolf; and associated the drug with this site due to the presence of transporters belonging to the solute carrier family 22 (SLC22) called human organic ion transporter-1 (hOAT-1) and adenosine triphosphate-binding cassette transporter family member called multidrug resistance protein-4 (MRP-4). These are transporters of TDF from the blood circulation into the proximal tubule intracellular space and secreting the drug into the urinary space respectively [20-21]. TDF demonstrated high efficacy in HIV-infected patients along with renal and bone adverse effects [22].

The renal toxicity of TDF occurs as a result of both or one of (i) excessive proximal tubular uptake of TDF from blood by hOAT-1 which accumulates the drug intracellularly (proximal tubule cell) and (ii) following disrupted secretion of TDF into the urine by MRP-4 that also poses a risk to accumulation of the drug inside proximal tubule cell. According to Kohler et al. the expression of kidney transporters may vary between individuals and also due to certain genetic regulation and down-regulation of genes that encode for transporters’ synthesis by TDF [23]. Lerma and Nissenson; and Fernandez-Fernandez et al. contend that the most common renal toxic effects of TDF are acute kidney injury and Fanconi syndrome; rarely nephrogenic diabetes insipidus [24-25].

1.3. Conceptual Framework

The conceptual framework for the study contended the clinical outcomes in terms of changes in body weight, and CD4 cell count; renal safety relative to changes in serum creatinine concentration, creatinine clearance and eGFR were evaluated in patients taking TDF-containing HAART regimens with respect to their treatment duration, baseline body weight, sex and age at antiretroviral initiation.

2. Methods

2.1. Study Design

The study followed a descriptive, observational, longitudinal retrospective design that evaluated the clinical outcomes and renal toxicity of TDF-containing HAART regimens.

2.2. Setting

The study was conducted at a primary health care facility called Paballong HIV/AIDS care centre located in Berea district in Lesotho. Primary health care facilities in Lesotho presently provide voluntary counselling and testing (VCT), antiretroviral therapy services, treatment for opportunistic diseases and counselling of patients and the caregivers for HIV/AIDS patients.

2.3. Study Population and Sampling Strategy

The target population included all HIV/AIDS patients who were served by the centre since 2014 and backwards. The population of patients on antiretroviral therapy was estimated at 600 patients in the year 2014. More than 50% of these patients were initiated on TDF-containing HAART regimens. According to Lesotho HIV/AIDS treatment guidelines, TDF
is a first-line drug and many adult patients are initiated on a TDF-based regimen after phasing out d4T due to toxicity profile [26].

The study population entailed both HIV-infected adult males and females aged \( \geq 18 \) years who weighed \( \geq 35 \) kg at baseline and attended the study site. Most of these patients resided in the villages that surround the facility and neither ethnicity nor language characteristics were used in selecting the participants. The study sample was obtained by taking a convenience sample from the HIV/AIDS patients served by the centre who complied with the inclusion and exclusion criteria.

2.4. Data Collection

The researchers designed the data collection tool that was used to capture the data. The data were obtained from patients’ medical records kept at the facility. This data archive consisted of files of each patient who was served by the facility for every clinical encounter made. The data included information on patient demographic information, baseline and follow-up clinical and laboratory data on physical examination; and anti-retroviral therapy regimens initiated and their durations.

2.5. Pilot Test

The validation was done by capturing data using the first 10 files at the study site before major data collection. In these files, it was evaluated roughly whether the tool captured majority of the variables that were needed. Indeed, the tool captured most of the required data. Therefore the large scale data gathering proceeded.

2.6. Main Study

The process of data collection using the data collection form proceeded from October 2015 to March 2016. The database was then prepared on a 2007 Microsoft® Excel® sheet and exported to the International Business Machines Statistical Package for the Social Sciences (IBM® SPSS®) Version 22® Statistical software [27].

2.7. Validity and Reliability

The information documented in the patients’ medical records was information entered by the nurse in charge and the laboratory findings from tests done. The nurse entered important information such as the date of birth, WHO clinical HIV/AIDS stage, body weight, sex, dates and regimens initiated. Laboratory results were obtained from the district laboratory where they were generated according to the national laboratory standard operating procedures (SOPs), irrespective of the researcher’s attention [28].

Demographic information and other measurements were generated by the relevant personnel working in the centre. The researcher himself was the one capturing the data from the files to the collection tool as accurately as they were made available. The mathematical analyses of the data applied the internationally accepted equations for renal function.

2.8. Ethical Considerations

Ethical approval was first obtained from the Ministry of Health Research and Ethics Committee, Lesotho (ID43-2014). The protocol was later approved by the Health Research Ethics Committee of the Faculty of Health Sciences at the NWU (NWU-00084-15-S1). Ultimately, permission to issue informed consent forms to patients and collect data was granted by the management of the Paballong HIV/AIDS care centre upon submission of ethical approvals from Ministry of Health Research and Ethics Committee and NWU Health Research Ethics Committee by the researchers. The project began as soon as when these ethical requirements were met.

2.9. Data Analysis

The data collected was summarised using descriptive statistics. Discrete was prepared in categories and percentages from the categories, while continuous data was firstly categorised into intervals and percentages were derived from the intervals. The standard deviation for the mean and the inter-quartile range for the median were used as measures of dispersion at 95% confidence level.

The specific objectives determined the change in variables over treatment duration, which means that there were observations of the variables recorded on patients’ files at baseline, during treatment and at end-time. The minimum time points and they included the baseline and at least one follow-up point; while the maximum time point included the baseline and follow-up points during treatment relatively at six-month interval and the end-time point which was the last observation of the follow-up.

Using the Shapiro-Wilk test, a normality test was done to evaluate whether the continuous data emanated from a normally distributed population or skewed distributed population. According to the test, \( p \)-values \( \geq 0.05 \) showed normal distribution while \( p \)-values < 0.05 showed that the data is either skewed to the right (positive) or skewed to the left (negative) [29].

In order to adjust for missing data and fitting the data based on assumptions, linear mixed statistical modelling was done and linear regression analysis was performed on the data. The analysis evaluated the effect of one independent variable on the change in the dependent variable at a time. The combined effect of the identified independent variables was also evaluated per dependent variable. For all the dependent variables, their change relative to the independent variables was determined from baseline observations to end-line observations over the treatment duration. The vector quantity was used to show declines and increments, that is, negative value changes showed declines in the dependent variable while positive values changes showed increments in the dependent variable.

The \( p \)-value of 0.05 was used as a measure of statistical
significance for the change in the dependent variable relative to identified independent variable(s) over treatment duration. The \( p \)-value of \( \leq 0.05 \) indicated the statistically significant change while there was no statistically significant change at \( p \)-values > 0.05.

3. Results

3.1. Demographic Data

The demographic data of the participants are presented in the Tables 1 and 2. Two hundred fifty-five participants were enrolled in the study (56.10% females, \( n=143 \)); with the mean age of 39.76 (11.93) years and 59.00 (12.87) kg mean baseline body weight. Most participants were initiated antiretroviral treatment at World Health Organization (WHO) clinical stage II (69.80%, \( n=178 \)). Most patients were initiated with TDF/lamivudine (3TC)/efavirenz (EFV) (84.70%, \( n=216 \)) HAART regimen. The baseline mean CD4 cell count and serum creatinine concentration were 328.16 (84.70%, \( n=216 \)) and 53.25 (37.50) µmol/l respectively. Seventy-three participants (28.60%) were on antiretroviral therapy for > 42 months.

### Table 1. Characteristics of the study participants.

| Variable (N=255) | Category | N (%)  |
|------------------|----------|--------|
| Sex              | Female   | 143 (56.10) |
|                  | Male     | 112 (43.90) |
| Age at initiation (years) | ≥18 to ≤40 | 141 (55.29) |
|                  | >40      | 114 (44.71) |
|                  | ≥0 to ≤12| 63 (24.71)  |
|                  | >12 to ≤24 | 55 (21.57)  |
|                  | >24 to ≤36| 48 (18.82)  |
|                  | >36      | 89 (34.90)  |
|                  | ≥35 to ≤50| 55 (21.57)  |
| Body weight (kg) | >50 to ≤80| 186 (72.94) |
|                  | >80      | 14 (54.90)  |
|                  | Stage I  | 9 (3.50)    |
|                  | Stage II | 178 (69.80) |
|                  | Stage III| 67 (26.30)  |
|                  | Stage IV | 1 (0.40)    |
| WHO HIV/AIDS Clinical stage | TDF/3TC/NVP | 22 (8.60) |
|                  | TDF/3TC/EFV | 216 (84.70) |
|                  | d4T/3TC/NVP* | 5 (2.00)   |
|                  | d4T/3TC/EFV* | 7 (2.70)   |
| ART regimen initiated | AZT/3TC/NVP* | 2 (0.80) |
|                  | AZT/3TC/EFV* | 2 (0.80)   |
|                  | ABC/3TC/EFV* | 1 (0.40)   |

### Table 2. Continuous data of the study participants.

| Variable (N=255) | Mean (SD) | Median (IQR) | 95% CI Lower Bound | 95% CI Upper Bound |
|------------------|-----------|--------------|---------------------|---------------------|
| Age at initiation (years) | 39.76 (11.93) | 38.00 (30.00-48.00) | 35.78-43.74 |
| Treatment duration (months) | 31.25 (20.99) | 27.00 (13.00-50.50) | 28.67-33.83 |
| CD4 cell count (cells/mm³) | 328.16 (167.25) | 308.00 (201.50-433.50) | 272.40-383.93 |
| Body weight (Kg) | 59.00 (12.87) | 56.000 (50.5-63.50) | 54.71-63.29 |
| Serum creatinine concentration (µmol/l) | 83.39 (37.50) | 78.000 (66.00-87.00) | |

3.2. Clinical Outcomes

The results in Table 3 unveil that females have more increment in body weight over treatment duration than males (\( p < 0.05 \)). In both males and females, there is also an increase in body weight over treatment duration relative to the age at antiretroviral therapy (\( p < 0.05 \)). This table infers that when body weight is evaluated from the combined effect of sex and age at ART initiation, on average females gained weight from 56.57 kg to 59.30 kg (56.57 kg +2.64 *1 + 0.10 *1 + (-.003) *1 year) at any age over one year of treatment. Males also gained weight but to a lesser extend from 56.57 kg to 59.30 kg (56.57 kg + 2.64 * 0 + 0.10 * 1 + (-.003) * 1 year) at any age over one year of treatment.

### Table 3. Body weight according treatment duration, sex and age at antiretroviral therapy initiation.

| Parameter                  | Estimate | Std. Error | df | \( t \) | \( p \)-value | 95% Confidence Interval |
|---------------------------|----------|------------|----|--------|--------------|-------------------------|
| Intercept                 | 56.57    | 0.80       | 5414.89 | 70.75 | 0.00        | 55.10 - 58.13            |
| Treatment duration        | -0.003   | 0.002      | 188.66 | -1.26 | 0.21        | -0.01 - 0.002            |
| Female                    | 2.64     | 0.39       | 5413.30 | 6.83  | 0.00        | 1.89 - 3.40              |
| Male                      | 0        | 0          | 5414.39 | 5.52  | 0.00        | 0.06 - 0.13              |
| Age at ART initiation     | 0.10     | 0.017      | 5414.39 | 5.52  | 0.00        | 0.06 - 0.13              |

Table 4 displays a statistically significant increase in CD4 cell count in both sexes (\( p<0.05 \)). Females have more increment in CD4 cell count than males over treatment duration. There is also a statistically significant increase in CD4 cell count due to age at antiretroviral therapy initiation over treatment duration (\( p < 0.05 \)). These results portray that when the change in CD4 cell count is evaluated from the combined effect of sex and age at ART initiation, females experienced increase in CD4 cell count from 179.67 cells/mm³ to 250.32 cells/mm³ (179.67 cells/mm³ + 69.13 * 1 + 1.32 * 1 + 0.20 * 1 year) at any age annually over treatment. Males have however experienced lesser elevations in CD4 cell count over one year of treatment from 179.67 cells/mm³ to 181.19 cells/mm³ (179.67 cells/mm³ + 69.13 * 0 + 1.32 * 1 + 0.20 * 1 year) at any age.
3.3. Renal Safety

The results in Table 5 show that although there is a decline in the estimated glomerular filtration rate over treatment duration in both sexes, there is worsened decline in females than males \((p < 0.05)\) and also decline in relation to age at antiretroviral therapy initiation \((p < 0.05)\) and body weight over one year treatment duration at a 95% confidence level \((p < 0.05)\).

3.4. Discussions

The results of the study revealed that over the treatment duration from initiation of antiretroviral therapy at any age, patients gained weight significantly from the baseline levels \((p < 0.05)\). The weight gain was estimated to 0.10 kg over the treatment duration in both sexes. Females were found to be the most advantageous to gaining more weight than males, with an estimated 2.64 kg more increase in weight gain \((p < 0.05)\). In overall, females gained weight from 56.57 kg to 59.30 kg while males gained weight from 56.57 kg to 56.67 kg over one year of treatment. The initiation of antiretroviral therapy in HIV/AIDS patients is associated with progressive clinical improvements including significant weight gain from baseline levels over treatment duration [30-31]. While the weight gain is observable in both males and females initiated on antiretroviral therapy, there is a greater increase in body weight among females than males [5, 33, 34].

The initiation of antiretroviral therapy was also associated with significant immunological improvements characterized by elevations in CD4 cell count from baseline findings \((p < 0.05)\). Patients initiated on antiretroviral therapy had an estimated 0.20 cells/mm\(^3\) increase in CD4 cell count over the treatment duration. The initiation of antiretroviral therapy at any age predicted an estimated 1.32 cells/mm\(^3\) increment in CD4 cell count over the treatment duration in both males and females \((p = 0.02)\). In contrast to males, females experienced an estimated 69.13 cells/mm\(^3\) added increase in CD4 cell count over the treatment duration. Generally, females experienced increase in CD4 cell count from 179.67 cells/mm\(^3\) to 250.32 cells/mm\(^3\) while males had elevations in CD4 cell count over one year of treatment from 179.67 cells/mm\(^3\) to 181.19 cells/mm\(^3\) over one year of treatment.

According to Maskew et al. HIV infected patients initiated on antiretroviral therapy had elevations in median CD4 cell count from 100 to 443 cells/mm\(^3\) in females and from 81 to 353 cells/mm\(^3\) for males over 36-month antiretroviral therapy treatment duration [35]. Although CD4 cell count elevation was observed in both sexes, females were found to have 2.7 times greater opportunity to attain CD4 cell count to \(\geq 350\) cells/mm\(^3\) than males over the treatment duration [36]. Again, females had the lowest risk of developing immunological failure than males in a systematic review done by Castillo et al., with 0.83 pooled risk ratio with reference to males [37].

Direct calculation of glomerular filtration rate was used in the analysis. The MDRD study equation showed a compromised renal function relative to age at antiretroviral therapy initiation, sex and body weight. The equation showed a significant decline of 0.78 ml/min in the eGFR at any age of antiretroviral therapy initiation in both sexes \((p < 0.05)\) over the treatment duration. When compared to males, females had significant 13.05 ml/min reduction in eGFR over the treatment duration \((p < 0.05)\). The equation disproved the improved GFR obtained in direct serum creatinine concentration measurement and creatinine clearance analysis above relative to weight gain. Instead, although not statistically significant, the body weight predicted 0.02 ml/min daily decline in estimated glomerular filtration rate over treatment duration \((p = 0.80)\). In summary, reductions in estimated glomerular filtration rate following yearly treatment were observed greater in females from baseline to
129.99 ml/min/1.73m² than in males whereby estimated glomerular filtration rate declined to 143.84 ml/min/1.73m².

According to Poggio et al. and Stohr et al., there exist differences in glomerular filtration rate between females and males and between the old and younger aged patients on antiretroviral therapy [38-39]. The retrospective analysis of change in eGFR at 6, 12 and 24 months following TDF HAART regimen initiation using MDRD study equation revealed progressive renal toxicity. The analysis showed hazard ratios of developing renal disease of 0.98 annually over treatment duration, 1.85 at every 10-year age increase and 1.63 and 1.00 in females and males respectively [40]. Therefore, the longer the treatment duration with aging and for females mostly, the more the risk of developing renal disease progressively.

5. Conclusion and Recommendation

In conclusion, clinical outcomes manifesting by weight gain and CD4 cell count elevation improve upon initiation of antiretroviral therapy at any age. Females are far more at advantage to experience better clinical outcomes than males over the treatment duration. The renal function is progressively deteriorated following initiation of antiretroviral therapy at any age. Females experience more renal compromise than males.

With these findings, the study recommends that regular clinical monitoring is key for efficacy and safety in the context of patients’ sex, age at treatment initiation and treatment duration in patients on TDF-containing regimens. Therefore periodic review for efficacy and safety should be done so as to make proper treatment switching when need arises; avoiding a generalised treatment approach to HIV-infected population which could ignore important parameters that may predict outcomes. Further studies on TDF-containing regimens should evaluate treatment outcomes with other parameters including plasma viral load and safety concerns on skeletal system since TDF-containing regimens do not only affect kidneys negatively; but also compromise bone mineral density.

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References

[1] Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA, 2004; 292 (2): 191-201.

[2] Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med, 2006; 324 (3): 251-260.

[3] Chua AC, Llorin RM, Lai K, et al. Renal safety of tenofovir containing antiretroviral regimen in a Singapore cohort. AIDS Res. Ther, 2012; 9: 1-5.

[4] Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-Infected patients. Clin. Infect. Dis., 2010; 51: 496-505.

[5] Crum-Cianflone N, Ganasan A, Teneza-Mora N, et al. Prevalence and factors associated with renal dysfunction among HIV-infected patients. AIDS patient care st, 2010; 24 (6): 353-360.

[6] Johnson DC, Chasela C, Maliwchi M, et al. Tenofovir use and renal insufficiency among pregnant and general adult population of HIV-infected, ART-naive individuals in Lilongwe, Malawi. PloS one, 2012; 7 (7): 1-7.

[7] Kalyesubula R & Perazella MA. Nephrotoxicity of HAART. Hindawi: 2011; 1-11.

[8] Sadre A, Munshi N, Dhande S, et al. Tenofovir-induced acute kidney injury in HIV-infected patients in western India: a resource limited setting perspective. JIAS, 2012; 15: 1.

[9] United Nations Programme on HIV/AIDS. Access to antiretroviral therapy in Africa: status report on progress towards the 2015 targets. 2013. http://www.unaids.org/sites/default/files/media_asset/20131219_AccessARTAfricaStatusReportProgressTowards2015Targets_en_0.pdf Date of access: 13 Nov. 2016.

[10] World Health Organization. Treat all people living with HIV, offer antiretrovirals as additional prevention choice for people at "substantial" risk. 2016b; http://www.who.int/mediacentre/news/releases/2015/hiv-treat-all-recommendation/en/ Date of access: 15 Mar. 2016.

[11] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2016c; http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1 Date of access: 13 Nov. 2016.

[12] United States of America. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016; http://aidsinfo.nih.gov/guidelines Date of access: 15 Sep. 2016.

[13] Kalajian RC, Lau B, Mechekano RN, et al. Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care. J Acquir Immune Defic Syndr, 2012; 26 (15): 1907-1915.

[14] Avihingsanon A, Gatechompol S, Sapsirisavat V, et al. Efficacy and safety of a once-daily single-tablet regimen of tenofovir, lamivudine, and efavirenz assessed at 144 weeks among antiretroviral-naive and experienced HIV-1-infected Thai adults. Int J Infect Dis, 2017; 61: 89-96.

[15] Louie M, Hogan C, Hurley A, et al. Determining the antiviral activity of tenofovir disoproxil fumarate in treatment-naive chronically HIV-1-infected individuals. J Acquir Immune Defic Syndr, 2003; 17 (8): 1151-1156.

[16] Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes-a 96-week analysis. J Acquir Immune Defic Syndr, 2006; 43 (5): 535-540.
[17] Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients 144-week analysis. J Acquir Immune Defic Syndr, 2008; 47 (1): 74-78.

[18] Min IS, Lee CH, Shin IS, et al. Treatment outcome and renal safety of 3-year Tenofovir Disoproxil Fumarate therapy in chronic hepatitis B patients with preserved glomerular filtration rate. Gut liver, 2019 13 (1): 93-103.

[19] Woodward CLN, Hall AM, Williams IG, et al. Tenofovir-associated renal and bone toxicity. HIV med, 2009; 10: 482-487.

[20] Hagos Y & Wolf NA. Assessment of the role of renal organic anion transporters in drug-induced nephrotoxicity. Toxins, 2010; 2: 2055-2082.

[21] Kohler JJ, Hosseini SH, Hoying-Brandt A, et al. Tenofovir renal toxicity targets mitochondria of renal proximal tubules. Lab invest, 2009; 89 (5): 513-519.

[22] Post FA, Yazdanpanah Y, Schembri G, et al. Efficacy and safety of emtricitabine/tenofovir alafenamide (FTC/TAF) vs. emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a backbone for treatment of HIV-1 infection in virologically suppressed adults: subgroup analysis by third agent of a randomized, double-blind, active-controlled phase 3 trial. HIV Clin Trials, 2017; 18 (3): 135-140.

[23] Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. Lab invest, 2011. 91 (6): 852-858.

[24] Lerma EV & Nissenson A. Nephrology secrets. 3rd ed. Philadelphia, PA: Mosby. 2012.

[25] Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat, 2011; 2 (1): 21-33.

[26] Castilho JL, Melekhin VV & Sterling TR, et al. Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review. AIDS res hum retroviruses, 2014; 30 (5): 446-456.

[27] Stohr W, Walker AS, Munder P, et al. Estimating glomerular filtration rate in HIV-infected adults in Africa: comparison of Cockroft-Gault and modification of diet in renal disease formulae. Antivir. Ther, 2008; 13: 761-770.

[28] Pujari, S. N., Smith, C., Makane, A., Youle, M., Johnson, M., Bele, V., Joshi, K., Dabhade, D. & Bhagani, S. 2014. Higher risk of renal impairment associated with tenofovir use amongst people living with HIV in India: a comparative cohort analysis between Western India and United Kingdom. BMC Infect Dis, 12 (173): 1-7.

[29] Lesotho. Ministry of Health. National guidelines on the use of antiretroviral therapy for HIV prevention and treatment. 5th ed. Maseru. 2016.