Research Article

Improved immunological profile of HIV infected patients with renal abnormalities on antiretroviral therapy

Abstract

Background: Kidney damage appears to be a common complication of HIV infection in the modern era of antiretroviral therapy (ART). This cross sectional study evaluate the pattern, nature and character of elevation of two basic renal safety parameters (urinary uric acid and glucose) in over 57 HIV-infected patients exposed to tenofovir (TDF) (21), non-TDF (21) and drug naïve (15) patients.

Methods: Urinary uric acid and glucose were assessed at commencement (V1) and after 4wks (V2), and after 12wks (V3) of patient exposure to therapy. Clinical features of both groups were comparable at commencement. Uricosuria and glucosuria were defined as urinary uric acid and glucose≥0.1mg/dl and ≥1.0 mg/dl respectively.

Results: After 12 weeks of follow-up incidence of uricosuria and glucosuria were as as follows: [TDF (9), non-TDF (2) and drug naïve (3) (p=0.000)] and [TDF (9), non-TDF (3) and drug naïve (1) (p=0.000)] respectively. Fractional excretion of uric acid was also altered in the two treatment groups.

Conclusion: The results show that treatment of HIV-infected patients with a TDF-based regimen compared to a non-TDF-based regimen produce alterations in safety biomarkers of renal pathophysiology parameters (creatinine, glucosuria, Uricosuria and CD4) after a 12-weeks treatment period. In conclusion, TDF may be associated with subclinical renal tubular damage, inducing at a later stage major increased in urinary excretion of glucose and uric acid, as markers of early tubular injury.

Keywords: TDF, renal safety, HIV, early tubular injury

Introduction

The kidneys can be susceptible to antiretroviral drug toxicity because of their layout and function. A growing number of cross sectional reports and longitudinal studies have described an association between treatment with antiretroviral therapy and proximal tubular dysfunction or impaired glomerular filtration rate (GFR) in patients with human immunodeficiency virus (HIV) infection. Alterations on tenofovir secretion by proximal renal tubule may lead directly to a greater drug accumulation in the renal tubular cells and, consequently lead to proximal tubular damage and renal toxicity. Several studies have found that CKD is associated with increased mortality among HIV-infected individuals. Studies of TDF toxicity suggested that mitochondria were unlikely to be the targets. Studies by Hall et al. have consistently observed marked ultrastructural abnormalities in mitochondria in the proximal tubule in cases of TDF-induced Fanconi syndrome. Further evidence in support of the fact that mitochondria are the major targets of TDF toxicity in the kidney has been provided by 2 recent rodent studies. However, the animals were exposed to about twice the normal dose in humans when adjusted for body weight. Interactions with other nephrotoxic agents and/or underlying genetic polymorphisms in transporters might help explain why TDF accumulates in proximal tubule cells in some patients, but do not shed further light on the exact intracellular targets of toxicity. Finally, there is evidence that TDF is specifically toxic to mitochondria in the proximal tubule, and the exact mechanisms of this damage remain unknown till date.

Materials and methods

Study protocol

This longitudinal study started in June 2013 at the Antiretroviral (ARV) clinic of the University of Port Harcourt Teaching Hospital, a reference hospital for tropical infectious diseases located in Port Harcourt, Rivers State, Nigeria. 75 HIV-infected patients under regular follow-up were invited to participate in the study, as long as they could be allocated into any of the three groups. TDF Group: 25 HIV infected patients about to commence TDF based regimen, N-TDF group: 30 HIV infected patients about to commence non TDF based regimen and treatment naïve group: 20 HIV infected patients who have CD4 counts greater than 500cell/ul and are not about to commence ART. Complete data was recovered from 57 patients while 20 patients were lost to follow-up. Serum and blood samples were analyzed for routine chemistry and a complete blood count. The 24-h urine samples were centrifuged and sent to the central laboratory for evaluation of routine parameters (protein, and phosphate). In order to eliminate the effect of incorrect urine collection, all assayed parameters were expressed as ratio versus urinary creatinine. The spot urine sample was centrifuged and stored at −70°C until being tested for urinary markers. Carley et al. simple normograms for the calculation of sample size for clinical diagnostic study was used for the calculation of sample size for this study.
Statistical analysis

Continuous values are given as mean and standard deviation while categorical data are given as percentages. The three groups of patients analyzed were first compared using chi-squared for categorical data and parametric tests for continuous variables. The level of significance was 0.05. All statistical analyses were performed using SPSS v20.0 software package (SPSS inc., Chicago, Illinois, USA).

Ethical Consideration

The study was carried out in accordance with the Helsinki Declaration and commence only after approval was given by the University of Port Harcourt Ethics Committee (UPH/R&D/REC/067) and the University of Port Harcourt Teaching Hospital Ethical Committee (UPHT/ADM/90/S.II/VOL.X/486). All data generated were kept in strict confidentiality.

Results

Among these 57 enrolled patients, 21 (36.8%) initiated tenofovir-containing regimen, 21 (36.8%) initiated tenofovir-sparing regimen and 15 (26.4%) were antiretroviral Naïve patients. Baseline demographic characteristics and laboratory features were compared among the groups. The present study assessed incidence of uricosuria and glucosuria in patients on different ART regimens over a 12 weeks period: at commencement, after 4 weeks and after 12 weeks. At commencement, all the patients in the three groups were not on treatment. The mean ages of male and female participants were: 36.43 and, 30.97 years respectively, with a statistically significant difference of P = 0.001 (Table 1).

Uricosuria was defined as urinary uric acid ≥ 0.1mg/dl. (Table 2) shows uricosuria at commencement (visit 1), after 4 weeks (visit 2) and after 12 weeks (visit 3) of follow-up. Uricosuria in the different regimen groups at commencement were as follows; treatment naïve group 2 (3.5%), N-TDF group 1(1.8%) and TDF group 4 (7.0%). A total of 7 (12.3%) patients at commencement had uricosuria. The difference among the groups was not statistically significant (X²=2.010, P=0.366). After 4 weeks (visit 2) of exposure uricosuria was found to be higher in the TDF group 10 (17.5%) compared to the other groups, N-TDF 5 (8.8%) and Naïve group: 0. The difference among the groups was highly statistically significant (X²=10.340, P=0.006). On the whole 15(26.3%) patients presented with uricosuria after 4 weeks. (Table 2) also shows the prevalence of uricosuria after 12 weeks (visit 3) of exposure to therapy. After 12 weeks, uricosuria decreased in all three groups, but was still higher in the TDF group: 9 (15.8%) compared to N-TDF group: 3 (5.3%) and naïve group: 2 (3.5%). The total number of Patients presenting with uricosuria after 12 weeks [14 (24.6%)] decreased when compared to the number of patients after 4 weeks [15 (26.3%)], but the difference between the study groups was not statistically significant (X²=6.011, P=0.090). Glucosuria was defined as Urinary Glucose ≥ 1.0mg/dl. (Table 3) shows the incidence of glucosuria in the different ART regimen groups and at different times point to be as follows: at commencement [TDF 5 (8.8%), N-TDF 4(7.0%), Naïve 1(1.8%)], after 4 weeks [TDF 12 (21.1%), N-TDF 3 (5.3.0%), Naïve 4(7.0%)] and after 12 weeks [TDF 9 (15.8%), N-TDF 3 (5.3%), Naïve 1(1.8%)]. The difference between the groups after 12 weeks was statistically significant (X²=7.033, P=0.030). A total of 13 (22.8%) patients presented with glucosuria after 12 weeks. (Table 4) shows the CD4 counts/viral loads of the two groups to be as follows: TDF group [Baseline, 210.87/<1000 copies/ml, after 4 weeks 365.81/<100 copies/ml, after 12 weeks 601.05/<50 copies/ml], Non-TDF group [Baseline, 211.48/<1000 copies/ml, after 4 weeks 244.31/<1000 copies/ml, after 12 weeks 389.67/<100 copies/ml].

### Table 1: Age and gender characteristics of study population

| Sex         | No. of patients | Mean Age | Standard Error of Mean | Minimum Age | Maximum Age | % of Total patients | P-Value |
|-------------|-----------------|----------|------------------------|-------------|-------------|--------------------|---------|
| Male        | 21              | 36.43    | 1.84                   | 18          | 50          | 36.80%             | 0.001   |
| Female      | 36              | 30.97    | 1.01                   | 20          | 45          | 63.20%             | (ANOVA) |
| Total       | 57              | 32.98    | 0.99                   | 18          | 50          | 100.00%            |         |

### Table 2: Prevalence of uricosuria in the different ART-groups at different times point

|                      | Uricosuria (Naïve group) | Uricosuria (N-TDF group) | Uricosuria (TDF group) | Total % |
|----------------------|--------------------------|--------------------------|------------------------|---------|
| Before Commencement  | Absent 2 (3.5%)          | Absent 20 (35.1%)        | Absent 1 (1.8%)        | 7(12.3%)|
| After 4 weeks        | Absent 15 (26.3%)         | Absent 16 (28.1%)        | Absent 5 (8.8%)        | 10(17.5%)|
| After 12 weeks       | Absent 13 (22.8%)         | Absent 18 (31.6%)        | Absent 3 (5.3%)        | 14 (24.6%)|

### Table 3: Prevalence of glucosuria in the different ART-groups at different times point

|                      | Glucosuria (Naïve group) | Glucosuria (N-TDF group) | Glucosuria (TDF group) | Total % |
|----------------------|--------------------------|--------------------------|------------------------|---------|
| Before Commencement  | Absent 14 (24.6%)         | Absent 17 (29.8%)        | Absent 4 (7.0%)        | 10 (17.5%)|
| After 4 weeks        | Absent 11 (19.3%)         | Absent 18 (31.6%)        | Absent 3 (5.3%)        | 19 (33.3%)|
| After 12 weeks       | Absent 14 (24.6%)         | Absent 18 (31.6%)        | Absent 3 (5.3%)        | 13 (22.8%)|

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Discussion

Nephrotoxic drugs including antiretroviral therapy (ART), such as tenofovir have adverse effect on the proximal tubule of the kidneys. Severe renal dysfunction leading to end stage renal disease is associated with very high mortality especially in Africa where over 80% of these patients die due to insufficient facilities, poverty and late presentation of patients. Elevated serum and urinary uric acid levels has been shown to correlate with the frequency of nephroliathiasis, and 50% of patients with serum uric acid levels greater than 13mg/dL or urinary uric acid secretion higher than 1100mg/dL will form stones.\textsuperscript{13} Uric acid stones are radiolucent, and the urinary uric acid crystals are reddish-orange. Random ratio of urinary uric acid to creatinine level, higher than 1.0, is suggestive of acute uric acid nephropathy in HIV patients on HAART. A disproportionate elevation in serum uric acid levels also can be a diagnostic clue of uric acid nephropathy in HIV-infected patients. Moreover, since uric acid is highly reabsorbed at the nephron level, with a fractional excretion that usually does not exceed 10% of the filtered uric acid; an increase in urinary uric acid excretion is an early marker of proximal tubular dysfunction.\textsuperscript{14}

Glucose is normally not present in urine. When glucose is present, the condition is called glucosuria. It results from either, an excessively high glucose concentration in the blood, such as may be seen with people who have uncontrolled diabetes mellitus and a reduction in the “renal threshold”. When blood glucose levels reach a certain concentration, the kidneys begin to excrete glucose into the urine to decrease blood concentrations. Sometimes the threshold concentration is reduced and glucose enters the urine sooner, at a lower blood glucose concentration. Normoglycemic glucosuria is another element that suggests the presence of proximal tubular damage in HIV-infected patients. Our results show that exposure to tenofovir seem to be associated with an increased risk of tubular abnormalities, evidence by the evaluation of urinary markers of renal tubular damage in the presence of decreased immunological failure. The incidence of uricosuria and glucosuria was significantly higher in tenofovir-treated group than in tenofovir-unexposed ones 14 (24.6%) and 13 (22.8%) respectively after 12 weeks of exposure which agree with what had already been reported by Labarga et al.\textsuperscript{13}

An interesting finding in this study was the increased in mean CD4 counts (601.05) and decreased in viral load (<50/ml/copies) in the TDF group diagnosed with renal abnormalities after 12 weeks of treatment period. Our results suggest that patients treated with tenofovir and other nephrotoxic antiretroviral therapy have a better immunological outcome in the presence of increased renal abnormalities. A significant number (3.5%, p=0.004) of the antiretroviral Naïve patients developed renal disease, perhaps this finding may indirectly supports the idea that HIV itself might cause tubular damage to some extent, as has been suggested by others.\textsuperscript{15–17} and especially in blacks.\textsuperscript{18}

Table 4 Mean CD4 of the study population within 12 weeks

|                  | Non-TDF Group | TDF Group | Differences among groups |
|------------------|---------------|-----------|--------------------------|
|                  | Means (SD)/VL | Means (SD)/VL | (z-test, P-Value)         |
| Baseline         | 211.48 (64.5)/<1000 copies/ml | 210.87 (74.9)/<1000 copies/ml | 0.583                    |
| After 4 weeks    | 244.31 (58.2)/<1000 copies/ml | 365.81 (116.4)/<1000 copies/ml | 0                        |
| After 12 weeks   | 389.67 (68.6)/<100 copies/ml | 601.05 (94.3)/<50 copies/ml | 0                        |

Conclusion

There is need to identify renal dysfunction at a much earlier stage to prevent progression and so reduce possible mortality. Early finding can enable clinicians to stratify patients on the basis of drug therapy, sidestepping nephrotoxic drugs and thereby reducing pervasiveness of overt renal dysfunction. In conclusion, the present study shows that HIV-infected exposed to antiretroviral therapy such as tenofovir seem to have more extensive tubular damage evidence by urinary elevation of uric acid and glucose. Most outstandingly this dysfunction evidence by uricosuria and glucosuria could be advanced especially in the group of patients treated with tenofovir (TDF).

Acknowledgment

None.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

Author’s contributions

DN conceived, designed and performed the experiment. KD wrote the manuscript and analysed the data. BA contributes to data interpretation, collection of samples and contributed reagents, materials and analysis tools. All authors read and approved the final manuscript.

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