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# Renal tubular disease and the relationship with tenofovir and atazanavir exposure

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## Background

- Renal tubular dysfunction is common in HIV positive patients treated with antiretroviral therapy (ART).
- Previous studies reporting on renal tubular pathology in HIV have been either limited by case numbers [1-3], or restricted to cases of interstitial nephritis [4-5] or tenofovir (TDF) induced renal tubular disease (RTD) [2]

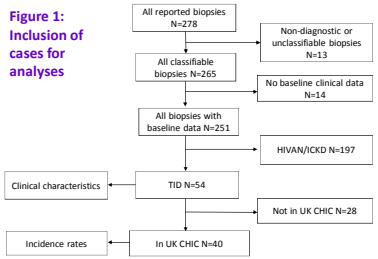
## Aims

- To describe the pathological spectrum of renal tubular disease (RTD), clinical characteristics at time of biopsy and a comparison of current and recent exposure to potentially nephrotoxic ART, including TDF, atazanavir (ATV), indinavir (IDV) and lopinavir (LPV)

## Methods

- 265 consecutive kidney biopsies between 1998 and 2012 in HIV positive individuals attending eight clinics in the UK were reviewed by a team of two histopathologists and one nephrologist blinded to clinical outcomes. Where reports were deemed equivocal or insufficient, sections were re-examined or, if unavailable, excluded (**Figure 1**)
- RTD was classified into 3 distinct patterns,
  - **Acute tubular injury (ATI**) when consistent histological changes were present either in isolation, or clearly disproportionate to any co-existent tubular or glomerular lesion
  - **Tubulo-interstitial nephritis (TIN),** which exhibited an appropriate mononuclear cell tubulo-interstitial infiltrate, with or without eosinophils, and not restricted to zones of chronic tubulo-interstitial damage
  - **Interstitial fibrosis and tubular atrophy (IFTA)** when consistent histological changes were present, with or without associated glomerulosclerosis, and in the absence of a distinct causative glomerular or tubulo-interstitial lesion
- We compared the clinical characteristics, including current or recent (up to 3 months prior to the biopsy) exposure to TDF, ATV, IDV and LPV, of patients with ATI, TIN and IFTA using Kruskal–Wallis tests, analysis of variance or Fisher's exact tests, depending on the distributions of the variables.
- We compared ART exposure frequency of patients with RTD with subjects from the same parent cohort who were diagnosed with immune complex kidney disease (ICKD) in the UK CHIC cohort [6] during the same period.
- We analysed the incidence of RTD by ART exposure in the UK CHIC cohort in those ever or never exposed to either TDF, ATV or LPV

**Figure 1: Inclusion of cases for analyses**




## Results

- 60/265 (22.6%) patients were diagnosed with RTD, of whom 54 (90%) had clinical information available. The clinical characteristics of patients with ATI (n=22), TIN (n=20) and IFTA (n=12) are shown in **Table 1**. ATI cases were less likely to be black (p=0.006) and more likely to be on ART (p=0.001) with HIV RNA <200 copies/ml (p<0.001) at biopsy as compared with TIN and IFTA.
- **Table 2** describes clinical outcomes of TID

## RTD characteristics, presentation and outcomes

**Table 1: Characteristics at baseline of TID**

| | | ATI (n=22) | TIN (n=20) | IFTA (n=12) | P value |
|---|---|---|---|---|---|
| Age (Years) | Mean (SD) | 50.6 (11.0) | 47.0 (11.9) | 49.9 (9.9) | 0.57 |
| Gender (Male) | N (%) | 21 (96) | 14 (70) | 11 (92) | 0.058 |
| Ethnicity (Black) | N (%) | 2 (10) | 11 (55) | 5 (42) | 0.006 |
| HIV risk (MSM) | N (%) | 3 (14) | 11 (58) | 6 (50) | 0.008 |
| HBV surface antigen positive | N (%) | 2 (10) | 1 (5) | 2 (17) | 0.62 |
| HCV Antibody positive | N (%) | 1 (5) | 2 (10) | 1 (8) | 0.83 |
| Time since HIV diagnosis (years) | Median (IQR) | 10.7 (7.0, 14.7) | 3.8 (0.2, 11.5) | 12.8 (0.3, 17.2) | 0.072 |
| On ART at biopsy | N (%) | 22 (100) | 11 (55) | 8 (67) | 0.001 |
| Current/recent use of TDF* | N (%) | 19 (86) | 4 (20) | 2 (17) | <0.001 |
| Past use of TDF | N (%) | 3 (14) | 0 | 1 (8) | 0.26 |
| Current/recent use of ATV* | N (%) | 4 (18) | 2 (10) | 3 (25) | 0.52 |
| Past use of ATV | N (%) | 4 (18) | 0 | 0 | 0.069 |
| Current/recent use of IDV* | N (%) | 0 | 1 (5) | 0 | 0.59 |
| Past use of IDV | N (%) | 6 (27) | 2 (10) | 3 (25) | 0.32 |
| Current/recent use of LPV* | N (%) | 8 (36) | 1 (5) | 3 (25) | 0.041 |
| Past use of LPV | N (%) | 3 (14) | 2 (10) | 0 | 0.52 |
| CD4 cell count nadir (cells/mm$^3$) | Median (IQR) | 154 (57, 245) | 102 (14, 210) | 87 (55, 176) | 0.42 |
| CD4 cell count (cells/mm$^3$) | Median (IQR) | 364 (240, 582) | 262 (131, 500) | 227 (123, 551) | 0.36 |
| AIDS | N (%) | 5 (24) | 7 (35) | 8 (67) | 0.056 |
| VL<200 copies/mL | N (%) | 22 (100) | 10 (54) | 7 (58) | <0.001 |
| Diabetes mellitus | N (%) | 7 (32) | 3 (15) | 1 (8) | 0.26 |
| Hypertension | N (%) | 9 (43) | 5 (26) | 6 (50) | 0.38 |
| eGFR (CKD-EPI, ml/min/1.73m$^2$) | Median (IQR) | 47 (10, 60) | 25 (16, 37) | 42 (32, 67) | 0.049 |
| Proteinuria (g/24h) | Median (IQR) | 1.4 (0.7, 2.2) | 1.8 (0.7, 2.3) | 1.2 (0.3, 4.8) | 0.91 |

*Stopped ≤ 3 months prior to biopsy

**Table 2: Clinical outcomes of TID**

| | | ATI (n=22) | TIN (n=20) | IFTA (n=12) |
|---|---|---|---|---|
| Renal syndrome* | Uprot >1.5 & eGFR <60 | 3 | 12 | 6 |
| | Uprot >1.5 & stable eGFR ≥60 | 3 | 0 | 0 |
| | Unexplained CKD | 3 | 3 | 1 |
| | Subacute eGFR decline | 0 | 0 | 3 |
| | AKI | 7 | 11 | 1 |
| | PRT | 5 | 0 | 0 |
| | Other | 1 | 0 | 1 |
| Suspected Aetiology* | Infection/drugs (non-ART) | 4 | 11 | 0 |
| | Malignancy/chemotherapy | 1 | 1 | 0 |
| | Other | 0 | 3 | 1 |
| | ART drugs (ATV, IDV) | 5 | 2 | 1 |
| | ART drugs (TDF) | 20 | 0 | 0 |
| | Unclear | 1 | 3 | 10 |
| Management* | Immunosuppression** | 2 | 11 | 0 |
| | TDF discontinued*** | 20 | 4 | 1 |
| | ATV/IDV discontinued*** | 4 | 3 | 2 |
| | RRT | 5 | 9 | 1 |
| Renal outcome (eGFR) | Return to baseline **** | 17 | 10 | 7 |
| | CKD3 (30-59) | 2 | 3 | 2 |
| | CKD4/5 (<30) | 2 | 1 | 1 |
| | ESKD | 1 | 5 | 2 |
| | Death | 3 | 3 | 1 |

*>1 possible, **Glucocorticoids (plus thalidomide, n=1), ***(incl. those who had already discontinued TDF/ATV) **** (eGFR >60 if no baseline)

## RTD and the relationship with ART

- 86% of patients with ATI had current/recent exposure to TDF as compared with 20% of patients with TIN and 17% of patients with IFTA (p<0.001).
- Compared with 64 ICKD cases (mean age 43.4 years, 66% male and 47% black ethnicity), patients with ATI were more likely to have current/recent exposure to TDF (odds ratio [OR] 9.8 [95% confidence interval 2.6, 36.7]), p<0.001), ATV (OR 7.8 [1.2, 50.2]), p=0.03) and LPV/r (OR 3.3 [1.0, 10.9], p=0.04). No ART associations were observed with TIN (p>0.2). IFTA was associated only with exposure to ATV (OR 10.3 [1.3, 79.7], p=0.03).
- 40 RTD cases (ATI [n=21], TIN [n=10], IFTA [n=9]) were identified in UK CHIC and included in the analysis. The incidence of ATI was somewhat higher among those ever (vs. never) exposed to TDF, ATV and LPV. No increased incidence of TIN or IFTA was observed. (**Table 3**)

**Table 3: Incidence of TID within the UK CHIC cohort**

| Event | | N | Person-years | Incidence /1000 yrs (95% CI) |
|---|---|---|---|---|
| ATI | **Ever TDF** | **17** | **143262.4** | **0.12 (0.06, 0.18)** |
| | No-TDF | 4 | 62000.4 | 0.06 (0.00, 0.13) |
| | **Ever ATZ** | **9** | **46265.2** | **0.19 (0.07, 0.32)** |
| | No ATZ | 12 | 158997.6 | 0.08 (0.03, 0.12) |
| | **Ever LPV** | **9** | **56181.9** | **0.16 (0.07, 0.30)** |
| | No LPV | 12 | 149080.9 | 0.08 (0.04, 0.14) |
| TIN | Ever TDF | 4 | 143262.4 | 0.03 (0.00, 0.06) |
| | No-TDF | 6 | 62000.4 | 0.10 (0.02, 0.17) |
| | Ever ATZ | 2 | 46265.2 | 0.04 (0.00, 0.10) |
| | No ATZ | 8 | 158997.6 | 0.05 (0.02, 0.09) |
| | Ever LPV | 4 | 56181.9 | 0.07 (0.02, 0.18) |
| | No LPV | 6 | 149080.9 | 0.04 (0.02, 0.09) |
| IFTA | Ever TDF | 5 | 143262.4 | 0.03 (0.00, 0.07) |
| | No-TDF | 4 | 62000.4 | 0.06 (0.00, 0.13) |
| | Ever ATZ | 3 | 46265.2 | 0.06 (0.00, 0.14) |
| | No ATZ | 6 | 158997.6 | 0.04 (0.01, 0.07) |
| | Ever LPV | 3 | 56181.9 | 0.05 (0.01, 0.16) |
| | No LPV | 6 | 149080.9 | 0.04 (0.02, 0.09 |

## Conclusion

- Renal tubular disease in HIV positive patients comprises a spectrum that includes ATI, TIN and IFTA with considerable clinical overlap.
- ATI was associated with exposure to cART in general and, more specifically, with exposure to TDF and ATV and accompanied by proximal tubulopathy in 23% of patients.
- We did not find evidence for an association between TIN and exposure to TDF, ATV or LPV and no consistent association between IFTA and ART exposure.
- Although 40% of cases were associated with exposure to TDF, ATV, IDV and LPV, the overall incidence of RTD remains low.

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