**Supplemental Content**.

**Supplemental Table 1**. EGFRcr estimates from multivariate linear mixed models using piecewise linear spline, year over year, assessing the association of TFV AUC with annual change in eGFRcr in mL/min/1.73 m2 (standard error) in WIHS HIV+ participants.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Category** | **Year 0** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** | **Year 7** |
| TFV AUC T1 | 104.0 (2.5) | 105.7 (2.3) | 107.3 (2.3) | 108.9 (2.4) | 109.1 (2.5) | 107.7 (2.6) | 106.3 (2.7) | 104.9 (2.9) |
| TFV AUC T2 | 94.6 (2.9) | 96.3 (2.8) | 98.0 (2.9) | 99.6 (3.2) | 99.3 (3.5) | 96.9 (3.7) | 94.5 (4.1) | 92.1 (4.5) |
| TFV AUC T3 | 80.0 (4.3) | 79.7 (4.2) | 79.5 (4.2) | 79.3 (4.3) | 78.2 (4.4) | 76.3 (4.5) | 74.4 (4.6) | 72.4 (4.9) |
| **UNADJUSTED DIFFERENCES IN eGFRcr** | | | | | | | | |
| T2 vs T1 | -9.4 (3.8), p=0.015 | -9.4 (3.7), p=0.012 | -9.3 (3.7), p=0.015 | -9.3 (4.0), p=0.023 | -9.8 (4.3), p=0.025 | -10.8 (4.5), p=0.021 | -11.7 (4.9), p=0.020 | -12.7 (5.4), p=0.021 |
| T3 vs T1 | -24.1 (5.0), p<0.0001 | -25.9 (4.8), p<0.0001 | -27.8 (4.8), p<0.0001 | -29.7 (4.9), p<0.0001 | -30.9 (5.1), p<0.0001 | -31.4 (5.1), p<0.0001 | -31.9 (5.4), p<0.0001 | -32.4 (5.7), p<0.0001 |
| **ADJUSTED\* DIFFERENCES IN eGFRcr** | | | | | | | | |
| T2 vs T1 | -6.2 (3.7), p=0.092 | -7.7 (3.4), p=0.028 | -9.1 (3.4), p=0.0096 | -10.5 (3.6), p=0.0049 | -11.2 (3.8), p=0.0047 | -11.2 (4.0), p=0.0073 | -11.2 (4.4), p=0.013 | -11.2 (4.8), p=0.024 |
| T3 vs T1 | -14.9 (5.1), p=0.0047 | -17.3 (4.9), p=0.0007 | -19.8 (4.8), p=0.0001 | -22.3 (4.9), p<0.0001 | -23.4 (5.0), p<0.0001 | -23.2 (5.0), p<0.0001 | -23.1 (5.2), p<0.0001 | -22.9 (5.6), p=0.0002 |

TFV = tenofovir; AUC = area-under-the-time-concentration-curve; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3; \*covariates in fully adjusted model include: age, race, body mass index, diabetes mellitus, hypertension, ritonavir use, duration of prior tenofovir exposure, and baseline CD4 cell count and HIV viral load

**Supplemental Table 2:** Association of TFV AUC with incident chronic kidney disease by various eGFRcr (mL/min/1.73 m2) thresholds in WIHS participants with HIV.

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Event Rate** | **Unadjusted**  **Incident Risk Ratio (95% CI)** | **Adjusted**  **Incident Risk Ratio (95% CI)** |
| **eGFRcr<50** | |  |  |
| **Continuous AUC:** |  |  |  |
| Per 10% increase | 4/101 (4.0%) | 1.37 (1.00, 1.87)  p=0.049 | n/a |
| **Categorical AUC:** |  |  |  |
| Tertile 1 | 0/35 (0%) | Reference | Reference |
| Tertile 2 | 1/34 (2.9%) | n/a | n/a |
| Tertile 3 | 3/32 (9.4%) | n/a | n/a |
| **eGFRcr<60** | |  |  |
| **Continuous AUC:** |  |  |  |
| Per 10% increase | 9/97 (9.3%) | 1.30 (1.14, 1.48)  p=0.0001 | 1.15 (0.93, 1.42)  p=0.19 |
| **Categorical AUC:** |  |  |  |
| Tertile 1 | 0/35 (0%) | Reference | Reference |
| Tertile 2 | 2/34 (5.9%) | n/a | n/a |
| Tertile 3 | 7/28 (25%) | n/a | n/a |
| **eGFRcr<70** | |  |  |
| **Continuous AUC:** |  |  |  |
| Per 10% increase | 12/90 (13.3%) | 1.18 (1.05, 1.34)  p=0.0068 | 1.22 (1.02, 1.46)  p=0.028 |
| **Categorical AUC:** |  |  |  |
| Tertile 1 | 2/35 (5.7%) | Reference | Reference |
| Tertile 2 | 4/34 (12%) | 2.06 (0.40, 10.5)  p=0.39 | 1.50 (0.33, 6.88)  p=0.60 |
| Tertile 3 | 6/21 (29%) | 5.00 (1.11, 22.6)  p=0.036 | 5.59 (1.25, 25.0)  p=0.025 |

Estimates from relative risk regression models. \*covariates in fully adjusted model: age, race, BMI, diabetes, hypertension, ritonavir, duration of prior TDF exposure, CD4 cell count, viral load.

**Supplemental Table 3**. EGFRcr estimates from multivariate linear mixed models using piecewise linear spline, year over year, assessing the association of TFV AUC category and baseline eGFRcr category with annual change and levels of eGFRcr (mL/min/1.73 m2) in WIHS HIV+ participants.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Category** | **Year 0** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** | **Year 7** |
| C1 | 105.5 (13.5) | 107.1 (12.6) | 108.6 (12.4) | 110.2 (13.0) | 110.6 (13.3) | 109.7 (13.4) | 108.9 (14.0) | 108.1 (14.9) |
| C2 | 105.4 (20.2) | 104.6 (20.7) | 103.9 (22.2) | 103.1 (24.5) | 101.7 (26.7) | 99.5 (28.6) | 97.3 (31.0) | 95.1 (33.8) |
| C3 | 89.1 (20.1) | 91.7 (18.9) | 94.3 (20.5) | 96.9 (24.4) | 96.1 (28.7) | 91.8 (33.3) | 87.5 (38.7) | 83.1 (44.6) |
| C4 (reference) | 70.6 (21.2) | 71.5 (20.9) | 72.4 (21.2) | 73.2 (22.3) | 72.6 (23.3) | 70.5 (24.2) | 68.4 (25.6) | 66.3 (27.6) |
| **UNADJUSTED DIFFERENCES IN LEVELS** | | | | | | | | |
| C1 vs. C4 | 34.9 (4.2), p<0.0001 | 35.6 (4.1), p<0.0001 | 36.3 (4.2), p<0.0001 | 36.9 (4.4), p<0.0001 | 37.9 (4.5), p<0.0001 | 39.2 (4.7), p<0.0001 | 40.5 (4.9), p<0.0001 | 41.8 (5.3), p<0.0001 |
| C2 vs. C4 | 34.8 (4.9), p<0.0001 | 33.1 (5.0), p<0.0001 | 31.5 (5.2), p<0.0001 | 29.9 (5.6), p<0.0001 | 29.0 (6.0), p<0.0001 | 29.0 (6.3), p<0.0001 | 28.9 (6.8), p=0.0002 | 28.9 (7.4), p=0.0006 |
| C3 vs. C4 | 18.5 (4.9), p=0.0005 | 20.2 (4.8), p=0.0001 | 22.0 (5.0), p<0.0001 | 23.7 (5.6), p=0.0001 | 23.4 (6.3), p=0.0007 | 21.3 (7.0), p=0.0047 | 19.1 (7.8), p=0.022 | 16.9 (8.9), p=0.068 |
| **ADJUSTED\* DIFFERENCES IN LEVELS** | | | | | | | | |
| C1 vs. C4 | 26.8 (4.7), p<0.0001 | 27.2 (4.5), p<0.0001 | 27.6 (4.5), p<0.0001 | 28.1 (4.7), p<0.0001 | 28.7 (4.8), p<0.0001 | 29.4 (4.9), p<0.0001 | 30.2 (5.2), p<0.0001 | 31.0 (5.5), p<0.0001 |
| C2 vs. C4 | 28.8 (5.2), p<0.0001 | 26.6 (5.1), p<0.0001 | 24.4 (5.2), p<0.0001 | 22.2 (5.5), p=0.0002 | 20.9 (5.7), p=0.0006 | 20.6 (5.9), p=0.0013 | 20.2 (6.2), p=0.0027 | 19.9 (6.7), p=0.0056 |
| C3 vs. C4 | 16.8 (4.2), p=0.0002 | 17.9 (4.0), p<0.0001 | 19.0 (4.4), p<0.0001 | 20.1 (5.0), p=0.0003 | 19.8 (5.7), p=0.0002 | 18.0 (6.4), p=0.0092 | 16.3 (7.3), p=0.035 | 14.5 (8.3), p=0.092 |

Tenofovir (TFV) area-under-the-time-concentration-curve (AUC) cutpoint for low vs. high category is based on median of 3.3 ｵg ﾗh/mL; C1= low TFV AUC & baseline (BL) BL estimated glomerular filtration rate by creatinine (eGFRcr, in mL/min/1.73 m2) >90, C2 = High TFV & BLeGFRcr>90, C3 = Low TFV & BLeGFRcr<90, C4 (reference) = High TFV & BLeGFRcr<90; \*covariates in fully adjusted model include: age, race, BMI, diabetes, hypertension, ritonavir use, duration of prior TDF exposure and baseline CD4 cell count and HIV viral load