Renal Function with Dolutegravir, Elvitegravir/ Cobicistat, Raltegravir or Darunavir

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Background

- Dolutegravir (DTG), raltegravir (RAL) and cobicistat (COBI) inhibit the tubular secretion of creatinine
  - Artificially lowers estimated glomerular filtration rate (eGFR)[1-3]
  - May lead to potential bias in renal impairment assessment
- Measurement error correction in the absence of sensitivity/specificity estimates is not well documented
- DTG, elvitegravir/c (EVG/c), RAL and darunavir (DRV) boosted with either COBI or ritonavir (RTV) are common core agents of antiretroviral therapy (ART)

OBJECTIVE

To assess the association between four common core agents (DTG, EVG/c, RAL or DRV) and renal impairment, with and without correcting for measurement error caused by the inhibition of tubular secretion of creatinine

Methods

Study population

- Inclusion criteria
  - HIV positive, ≥13 years of age
  - Start a new regimen with DTG, EVG/c, RAL or DRV between 1AUG2013 and 31DEC2016 (first exposure, only 1 core agent)
  - Baseline eGFR and proteinuria available
- Baseline date: date of regimen initiation
- Observation period: from regimen initiation until: (1) core agent discontinuation, (2) cessation of continuous clinical activity (censored 12 months after last contact), (3) death, or (4) study end (31 Dec, 2017)

Renal impairment

- History: 2 consecutive eGFR <60 mL/min per 1.73 m^2 ≥14 days apart, or eGFR <30, or acute kidney injury (AKI) diagnosis at or ≤12 months before baseline
- New renal impairment: eGFR <60 or AKI diagnosis (no history)

eGFR measurement

- CKD-EPI formula (2009) based on serum creatinine, sex and race
- eGFR correction: impact of inhibition of creatinine tubular secretion corrected based on the average eGFR decrease reported in the literature[1-3] (Table 3)

Statistical analyses

- Cox Proportional Hazard models
- Adjusted for age, sex, race, TDF, NSAID and sulfamethoxazole/trimethoprim use, hypertension, diabetes, hepatitis C, and abnormal renal function (i.e. eGFR <90 and/or proteinuria >1+) at baseline
- With and without eGFR correction

Results

Table 1. Baseline demographic characteristics

	Dolutegravir N= 5,465	Elvitegravir N= 5,941	Raltegravir N= 838	Darunavir N= 2,024
Age ≥ 50 years	1631 (29.8%)	1372 (23.1%)*	377 (45.0%)*	615 (30.4%)
Female	762 (13.9%)	837 (14.1%)	176 (21.0%)*	413 (20.4%)*
African-American	2171 (39.7%)	2460 (41.4%)	318 (37.9%)	972 (48.0%)*
Hispanic	1361 (24.9%)	1425 (24.0%)	140 (16.7%)*	410 (20.3%)*
U.S. Region: Southern states	2908 (53.2%)	3860 (65.0%)*	532 (63.5%)*	1267 (62.6%)*

* p-value <0.001 for the comparison with DTG

Table 2. Baseline clinical characteristics

	Dolutegravir N= 5,465	Elvitegravir N= 5,941	Raltegravir N= 838	Darunavir N= 2,024
ART-naïve	2004 (36.7%)	2439 (41.1%)*	151 (18.0%)*	704 (34.8%)
TDF	1451 (26.6%)	4099 (69.0%)*	588 (70.2%)*	1641 (81.1%)*
NSAID	391 (7.2%)	308 (5.2%)*	44 (5.3%)	156 (7.7%)
Sulfamethoxazole/ Trimethoprim	697 (12.8%)	741 (12.5%)	92 (11.0%)	477 (23.6%)*
Diabetes Mellitus	425 (7.8%)	309 (5.2%)*	119 (14.2%)*	156 (7.7%)
Hypertension	1382 (25.3%)	1210 (20.4%)*	290 (34.6%)*	479 (23.7%)
HCV Co-Infection	535 (9.8%)	330 (5.6%)*	119 (14.2%)*	216 (10.7%)
Renal Impairment History	232 (4.2%)	105 (1.8%)*	80 (9.5%)*	58 (2.9%)*
Impaired Renal Function (eGFR <90 or proteinuria > +1)	2789 (51.0%)	2739 (46.1%)*	554 (66.1%)*	1055 (52.1%)

* p-value <0.001 for the comparison with DTG

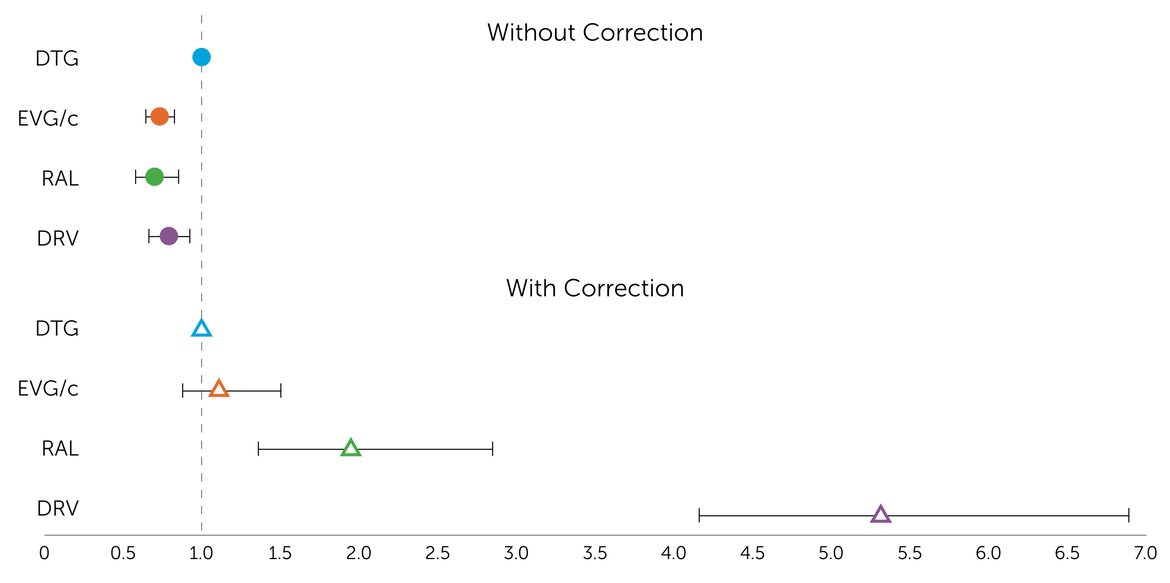
Results, Cont.

Table 3. Incident renal impairment over follow-up and association with core agents, before and after eGFR correction

	No eGFR Correction		eGFR Correction		
	Renal Impairment Events	Adjusted* Hazard Ratio aHR (95% CI)	Correction Factor	Renal Impairment Events	Adjusted* Hazard Ratio aHR (95% CI)
Dolutegravir (N=5,465)	695 (12.7%)	1.00 (ref)	eGFR+17	180 (3.3%)	1.00 (ref)
Elvitegravir (N=5,941)	440 (7.4%)	0.72 (0.63, 0.81)	eGFR+14	133 (2.2%)	1.14 (0.87, 1.51)
Raltegravir (N=838)	98 (11.7%)	0.66 (0.53, 0.82)	eGFR+9	53 (6.3%)	1.94 (1.36, 2.76)
Darunavir (N=2,024)	203 (10.0%)	0.77 (0.65, 0.91)	COBI: eGFR+11 RTV: NA	184 (9.1%)	5.32 (4.13, 6.85)

* Adjusted for baseline age, sex, race, TDF, NSAID and sulfamethoxazole/trimethoprim use, hypertension, diabetes, hepatitis C, and abnormal renal function (i.e. eGFR <90 and/or proteinuria >1+)

Figure 1. Adjusted* hazard ratios for the association between core agents and progression to renal impairment before (•) and after (Δ) eGFR correction**



* Adjusted for baseline age, sex, race, TDF, NSAID and sulfamethoxazole/trimethoprim use, hypertension, diabetes, hepatitis C, and abnormal renal function (i.e. eGFR <90 and/or proteinuria >1+)

** eGFR correction consisted of adding the correction factor listed to the eGFR calculated with the CKD-EPI 2009 equation (Table 3)

Discussion

- Inhibition of tubular creatinine secretion with common ARVs results in an inflated number of renal impairment events defined based on eGFR cut-offs
- Correcting for artificial lowering of eGFR had a substantial impact on the association between core agent initiation and development of renal impairment in multivariate models adjusted for other potential risk factors, including TDF
  - Suggests that many of the events observed before correction were driven by the inhibition of creatinine secretion and therefore might not be of clinical concern
- Limitations: did not account for the uncertainty around the exact level of inhibition experienced by patients on different regimens
  - Results only illustrate the potential extent of bias associated with uncorrected eGFR

KEY FINDINGS

- Some renal impairment events observed may not be of clinical concern due to the inhibition of creatinine tubular secretion by DTG, RAL and COBI
- eGFR correction had a substantial impact on the number of events and modeling results

References

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