EP056

Association between integrase inhibitors (INSTIs) and tenofovir alafenamide (TAF) and moderate chronic kidney disease (CKD) in the RESPOND HIV cohort collaboration

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Background

- CKD is more common amongst people with HIV vs the general population [1]
- CKD increases the risk of other comorbidities, e.g. cardiovascular disease, and of death [2,3]
- Use of several protease inhibitors (PIs) and tenofovir disoproxil fumarate (TDF) are associated with increased CKD risk [4-6]
- However, there is little data assessing use of INSTIs and TAF and CKD risk
- There may be an artefactual creatinine increase in the first months after starting INSTIs, rilpivirine, doravirine and boosted PIs
- We performed two separate incident CKD analyses:
  1. **INSTIs vs non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
  2. **TAF vs lamivudine (3TC),** with both comparator antiretrovirals (ARV) considered non-nephrotoxic

Methods

- **Inclusion criteria:** RESPOND participants ≥18 years, starting an ARV of interest after latest of local cohort enrolment and Jan 2012, with ≥2 estimated glomerular filtration rate (eGFR) measurements during follow-up
- **Exclusion criteria:** pre-existing CKD (as defined below) at treatment start, exposure to potentially nephrotoxic ARVs (atazanavir/b, indinavir, lopinavir/r, TDF) within 12 months of or at treatment start
- **Exposure group:** first ARV of interest in each analysis
- **Baseline:** 6 months after treatment start to account for the potential artefactual creatinine increase
- **End of follow-up:** earliest of CKD, starting a nephrotoxic ARV during follow-up, loss to follow-up, death, 31 Dec 24
- **Outcome:** CKD - 2 consecutive eGFRs*, measured ≥3 months apart:
  - ➢ <60 mL/min/1.73m² if baseline eGFR ≥ 60
  - ➢ ≥25% decline if baseline eGFR < 60

  *calculated using CKD Epi Collaboration equation
- **Statistical analysis**:
  - Median eGFR over time compared between groups
  - Multiple imputation with chained equations used to impute missing data
  - CKD risk compared using inverse probability of treatment weights (IPTW) to account for differences between treatment groups and pooled logistic regression

INSTI vs NNRTI Results

- 6276 were included on INSTIs, 1200 on NNRTIs
- Most common INSTIs: dolutegravir (58%), bictegravir (26%), raltegravir (8%)
- Most common NNRTIs: rilpivirine (40%), efavirenz (28%), nevirapine (21%)
- The majority in both groups included backbones abacavir/3TC (38% INSTI, 50% NNRTI) or TAF/emtricitabine (43%, 26%)
- At baseline, a higher proportion on INSTIs had suppressed viral load, hypertension (**Table 1**) and a higher D:A:D 5-year CKD risk (**Fig 1**)

TAF vs 3TC Results

- 3227 were included on TAF, 2424 on 3TC
- The most common 3rd drugs prescribed with TAF were bictegravir (42%), dolutegravir (19%), elvitegravir/c (15%)

  and with 3TC were dolutegravir (56%), darunavir/b (14%), efavirenz (14%)
- At baseline, a higher proportion on TAF had a suppressed viral load and prior comorbidities (**Table 1**) and a higher D:A:D 5-year CKD risk (**Fig 1**)

Table 1 Participant characteristics at baseline (6 months post treatment start)

	Analysis 1: INSTI vs NNRTI				Analysis 2: TAF vs 3TC			
	INSTI (n=6276)		NNRTI (n=1200)		TAF (n=3227)		3TC (n=2424)	
	n	(%)	n	(%)	n	(%)	n	(%)
Male sex/gender	4966	(79)	893	(74)	2621	(81)	1915	(79)
White race/ethnicity	4715	(75)	961	(80)	2396	(74)	1809	(75)
MSM HIV acquisition group	3397	(54)	593	(49)	1786	(55)	1335	(55)
HIV viral load <200cps/mL	5967	(95)	1060	(88)	3043	(94)	2137	(88)
Hypertension	3235	(52)	506	(42)	1715	(53)	816	(34)
Diabetes	398	(6)	77	(6)	245	(8)	104	(4)
Prior CVD	213	(3)	30	(3)	139	(4)	49	(2)
ART naive at treatment start	2528	(40.3)	499	(41.6)	1631	(50.5)	1636	(67.5)
	Median	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**
Baseline date	Dec18	(Jan17, Feb21)	Oct15	(Nov13, Jul28)	Oct19	(Jun18, Apr21)	Sept16	(Apr15, Apr18)
Age, years	47	(37, 55)	45	(36, 53)	46	(36, 55)	41	(33, 50)
CD4 count, cells/mm³	616	(416, 830)	593	(429, 784)	580	(377, 800)	567	(375, 780)
eGFR	92	(79, 105)	98	(84, 109)	94	(81, 107)	97	(84, 110)

Abbreviations: MSM-men who have sex with men; cps-copies; CVD-cardiovascular disease; ART-antiretroviral therapy; IQR-interquartile range

- Amongst 5967 participants with non-missing baseline eGFR:
  - Median follow-up was longer on NNRTIs (7.1 vs 5.1 years)
  - **296 participants developed CKD: 252 on INSTI (IR 9.7/1000 PYFU), 44 on NNRTI (IR 6.7/1000 PYFU)**
- Amongst those with CKD, median decline in eGFR from baseline to CKD diagnosis was relatively small **(Table 2)**
- Few individuals with CKD had an eGFR<30 during follow-up: 17 (7%) INSTI vs 7 (16%) NNRTI
- After multiple imputation of missing baseline eGFR, all participants were included in IPTW analysis (n=7476)
- After adjustment for potential confounders, there was no difference in CKD risk between use of INSTIs and NNRTIs:

  hazard ratio: 1.13 (95% CI 0.73, 1.76), p=0.58

  (Fig 2)

- Amongst 4571 participants with non-missing baseline eGFR:
  - Median follow-up was longer on 3TC (7.1 vs 4.8 years)
  - **198 participants developed CKD: 117 on TAF (IR 9.8/1000 PYFU), 81 on 3TC (IR 6.2/1000 PYFU)**
- Amongst those with CKD, median decline in eGFR from baseline to CKD diagnosis was relatively small (**Table 2**)
- Few individuals with CKD had an eGFR<30 during follow-up: 8 (7%) on TAF vs 6 (7%) on 3TC
- After adjustment for potential confounders and imputation (n=5651), there was no difference in CKD risk between use of TAF and 3TC:

  hazard ratio: 1.15 (95% CI 0.80, 1.65), p=0.45

  (Fig 2)

Figure 1 Estimated 5-year D:A:D CKD risk score at baseline stratified by ARV exposure

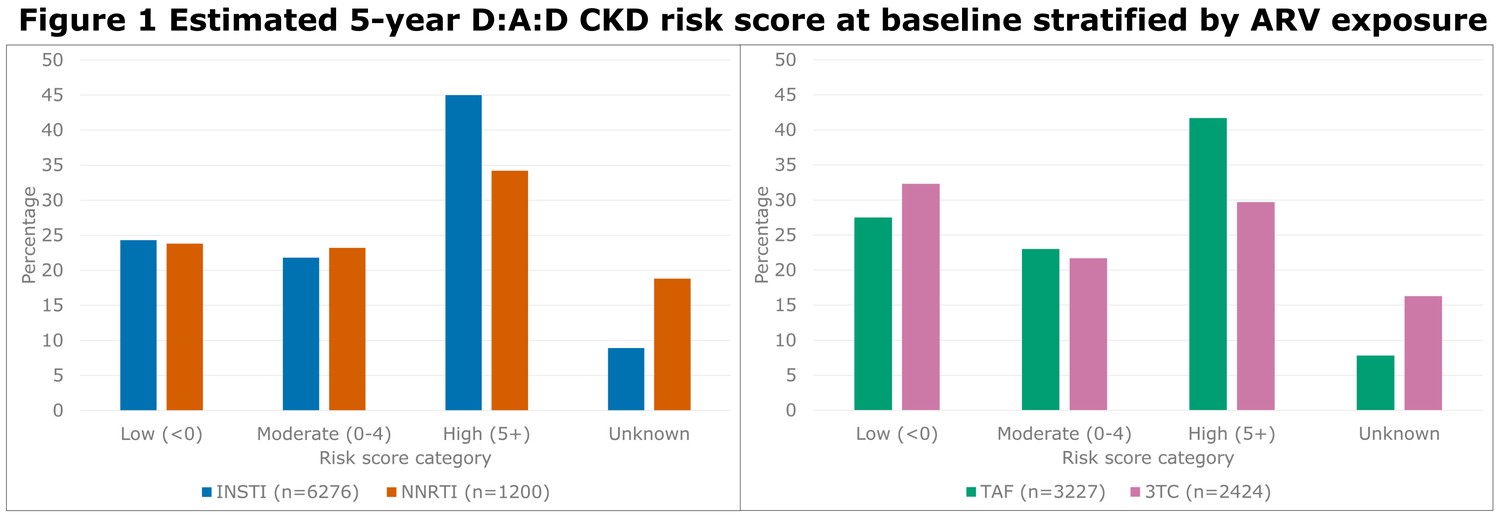
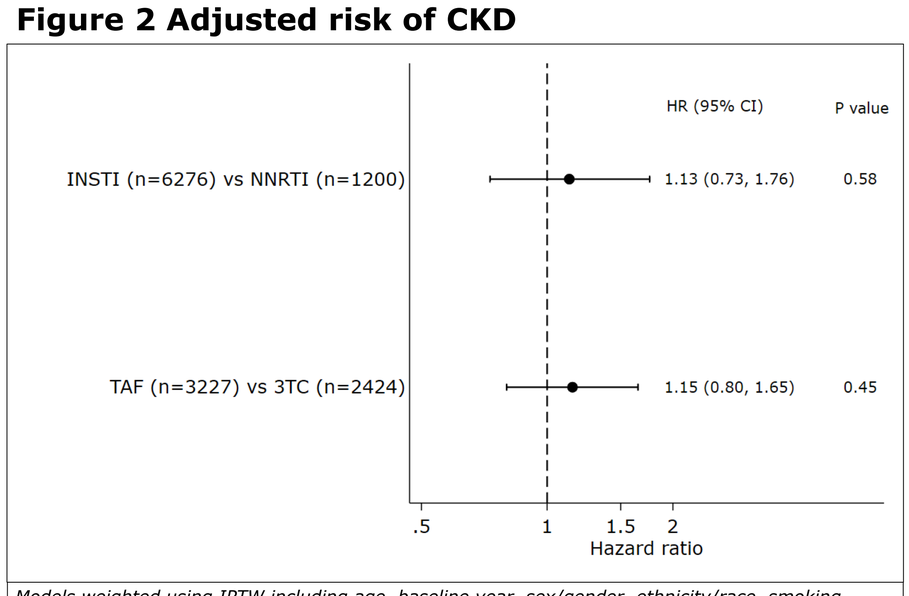


Figure 2 Adjusted risk of CKD



Models weighted using IPTW including age, baseline year, sex/gender, ethnicity/race, smoking status, RESPOND cohort, HIV acquisition group, body mass Index, CD4 count, nadir CD4, HIV viral load, hypertension, cardiovascular disease, diabetes, AIDS, hepatitis B, hepatitis C, HDL, total cholesterol, cumulative prior exposure to atazanavir/b, indinavir, lopinavir/r, TDF, and eGFR, all defined at baseline

Table 2 Changes in eGFR in those with CKD

	INSTI (n=252)	NNRTI (n=44)	TAF (n=117)	3TC (n=81)
Median (IQR) eGFR at treatment start	78 (71, 88)	78 (68, 94)	75 (67, 84)	82 (70, 92)
Median (IQR) eGFR at baseline (treatment start + 6 months)	69 (64, 77)	72 (66, 87)	69 (64, 76)	73 (67, 84)
N (%) with baseline eGFR=60-70	138 (55)	18 (41)	61 (52)	31 (38)
Median (IQR) eGFR at CKD	54 (49, 58)	55 (43, 58)	55 (50, 58)	54 (46, 58)
Median (IQR) decline in eGFR from baseline to CKD event	17 (9, 25)	21 (15, 35)	17 (12, 22)	21 (15, 33)
N (%) with eGFR <30 during follow-up	17 (7)	7 (16)	8 (7)	6 (7)
Median (IQR) nadir eGFR during follow-up	53 (47, 57)	52 (42, 57)	53 (49, 58)	53 (46, 57)

Limitations

- Lack of data on urinary markers, serum phosphate levels, family history of renal disease, other drugs with nephrotoxic potentials, creatinine supplements and substance use
- eGFR was estimated based on creatinine as actual GFR measurements and cystatin C not collected in RESPOND
- Although adjusted for calendar year, there remains the potential for other unmeasured confounding driven by earlier median calendar treatment start in comparator groups
- Median follow-up potentially too short to capture long-term renal effect of ARVs

Conclusions

- Using a large and diverse cohort, crude CKD incidence ranged from 6-10 per 1000 PYFU with **no evidence of adverse renal outcomes on INSTI or TAF**
- For those with CKD, **median decline in eGFR was relatively small** for all treatment groups and **few participants had an eGFR<30** during follow-up

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RESPOND Study Group:
https://chip.dk/Research/Studies/RESPOND/Study-group

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