078

Risk of fracture with contemporary antiretrovirals within the RESPOND Consortium

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RESPOND International Cohort Consortium of Infectious Diseases

Plain language summary

Whilst in our primary analyses, the use of integrase inhibitors and tenofovir alafenamide was associated with a small increase in fracture risk, this association was no longer evident after excluding the use of boosted protease inhibitors or tenofovir disoproxil fumarate, known to be associated with fractures, suggesting these findings are likely explained by treatment history and baseline risk.

BACKGROUND

- People with HIV have a higher fracture risk than those without HIV [1-4]
- Tenofovir disoproxil fumarate (TDF) and boosted protease inhibitors (PI/b) have been linked to increased fracture risk [5-7]
- The relationship between integrase strand transfer inhibitors (INSTIs) and/or tenofovir alafenamide (TAF) with fracture risk remains uncertain

METHODS

- We included RESPOND participants aged >18 years
- Baseline: First visit after the later of local cohort enrolment or 1 January 2012. Follow-up (FU): until the latest of the final visit or 31 December 2022
- Associations between established fracture risk factors and initiation of INSTI or TAF were assessed using logistic regression to evaluate potential confounding by indication
- Poisson regression with generalised estimating equations and robust standard errors estimated adjusted relative risk for fractures with ever exposure to INSTIs and TAF
- Sensitivity analyses excluded individuals with prior TDF and/or PI/b exposure and censored individuals who initiated either TDF or PI/b during follow-up

RESULTS

- A total of 40,244 participants were included (Table 1)
- Participants who experienced a fracture were older, current smokers, and more likely to have a low BMI, chronic kidney disease, HCV, or a prior fracture
- During a median follow-up of 8.4 years (301,862 person-years of follow-up), 2155 participants experienced one or more fractures (2,544 fractures in total)
- Lower leg fractures were the most prevalent, accounting for 375 fractures (14.7%)

Table 1: Baseline demographics and clinical characteristics by fractures during FU

	First Fracture after baseline		No Fracture	
	n	(%)	n	(%)
Total	2155	5.4	38089	94.6
Sex/gender				
Male	1604	74.4	28715	75.4
Ethnicity/race				
White	1718	79.7	27573	72.4
Black	135	6.3	4441	11.7
Geographical Region				
Western Europe	1227	56.9	17627	46.3
Southern Europe	250	11.6	6833	17.9
Northern Europe	555	25.8	8549	22.4
Eastern Europe	123	5.7	5080	13.3
HIV acquisition risk				
MSM	900	41.8	17995	47.2
IDU	398	18.5	4691	12.3
ART treatment history				
ART Experienced	1801	83.6	27475	72.1
ART Naïve	354	16.4	10614	27.9
Prior AIDS				
yes	615	28.5	7833	20.6
Smoking status				
Never	506	23.5	10573	27.8
Current	956	44.4	13311	34.9
BMI				
<18.5	932	43.2	15018	39.4
18.5-<25	144	6.7	2149	5.6
25-<30	475	22	7060	18.5
>30	103	4.8	1181	3.1
Co-morbidities				
HCV	592	27.5	7139	18.7
Hypertension	152	7.1	1411	3.7
Diabetes	190	8.8	2307	52.2
Dyslipidaemia	1383	64.2	19871	6.1
Prior fracture	96	4.5	806	2.1
Prior CVD	69	3.2	461	1.2
Continuous variables	Median	IQR	Median	IQR
Baseline CD4, cells/mm³	515	351 - 705	513	338 - 709
Age, years	49	42 - 56	44	35 - 51

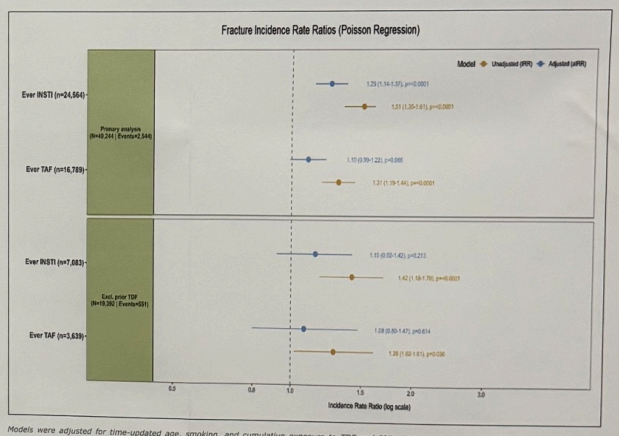
Percentage of overall unknowns: ethnicity: 15.9, Risk of HIV acquisition: 4.1, Prior AIDS: 5.4, BMI: 35.6, smoking status: 36.4, hypertension: 17.5, diabetes: 20.8, CKD: 9.8, and CVD: 9.8

References
[1]: Smiau et al. Aids, 2013 [2]: Goh et al. Osteoporosis International, 2018 [3]: Bedimo et al. 2016 [4] :Hoy et al. Journal of Bone and Mineral Research, 2017 [5]: Alvarez-Barco et al. Curr. Opin. HIV AIDS, 2021 [6]. Bedmo et a. Aids, 2012 [7]: Borges et al. Clinical Infectious Diseases , 2017

RESULTS

- There were 555 (21.8%) fractures at locations associated with osteoporosis (fractures of the spine, lower arm/wrist and hip)
- Prior fractures were not associated with INSTI initiation but showed a small association with TAF initiation (OR 1.08; 95% CI 1.02–1.15).
- Smoking status was significantly associated with INSTI and TAF initiation (1.26; 1.23-1.3 and 1.16; 1.12-1.20); eGFR <60 was borderline significant for both initiating INSTIs and TAF (1.05; 1.00-1.11 and 1.01; 0.95-1.07)
- Age >40 years compared to older age groups was associated with a lower likelihood of initiating either an INSTI or TAF (global p <0.001 for both)
- Ever exposure to INSTIs or to TAF was associated with a small increased relative fracture risk (Figure 1)
- After excluding those with prior TDF use and censoring at TDF initiation, the associations were no longer statistically significant. Similar findings occurred when excluding prior PI/b exposure and censoring at PI/b initiation

Figure 1: Crude and adjusted relative fracture risk with 95% CIs



Models were adjusted for time-updated age, smoking, and cumulative exposure to TDF and PI/b. Further, they accounted for baseline sex/gender, ethnicity/race, region, transmission mode, body mass index, CD4 count, nadir CD4 count, ART experience, HCV, hypertension, diabetes, dyslipidaemia, cancer, chronic kidney disease, fracture, AIDS, calendar time, and time since HIV diagnosis. Moreover, the model investigating INSTIs was further adjusted for ever TAF exposure, and the model investigating TAF for ever INSTI use.

LIMITATIONS

- Potential for confounding by indication, as seen, e.g., by prior fractures being associated with TAF initiation, and more smokers among those starting TAF and INSTI
- Possible residual confounding by unmeasured factors or factors not collected, such as menopause status or use of corticosteroids.
- A large number of fractures of unknown type and with unknown fracture location hampering differentiation of traumatic and osteoporotic fractures

CONCLUSION

- INSTI and TAF use were associated with a small increase in relative fracture risk in the primary analyses
- The attenuation observed after accounting for TDF and PI/b exposure suggests the findings are likely due to confounding by treatment history and baseline risk factors, rather than reflecting a safety signal

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

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