CROI 2016

Antiretrovirals, fractures and osteonecrosis in a large European HIV cohort

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* no financial relationships with commercial entities to disclose.

Background

- Fractures and osteonecrosis of the femoral head have emerged as important manifestations of bone disease during treated HIV infection
- HIV+ persons have 1.5-3.0-fold greater risk of fractures and 100-fold greater risk of osteonecrosis compared with the general population
- Initiation of antiretroviral therapy, in particular regimens containing tenofovir DF (TDF), is associated with increased levels of markers of bone turnover and reduction in bone mineral density. The clinical consequences of this have not been determined.
- The effect of antiretroviral exposure on the risk of fractures and osteonecrosis remains poorly understood.

Grund AIDS 2009
Morse CID 2007
Triant JCEM 2008
McComsey CID 2011
Bedimo AIDS 2012
Prieto-Alhambra JAIDS 2014

Objectives

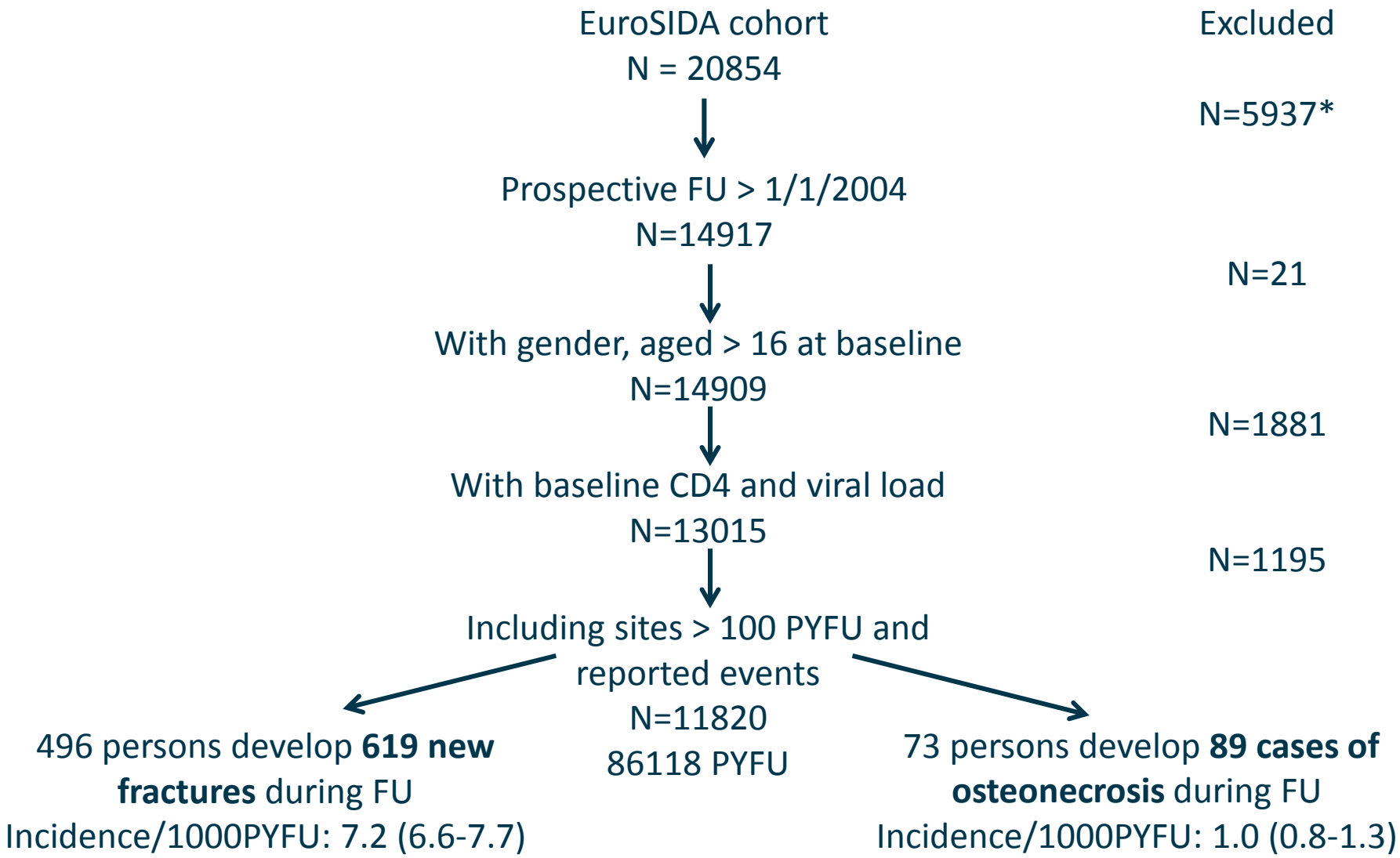
- To determine factors independently associated with incident fractures and osteonecrosis

- To study the association between exposure to antiretrovirals and subsequent risk of fractures and osteonecrosis

Methods

- Inclusion criteria: EuroSIDA participants >16 y with prospective follow up after 1 January 2004 and baseline data on CD4 and viral load
- Poisson regression with appropriate adjustments for multiple events per patient was used to identify clinical, laboratory and demographic factors associated with fractures and osteonecrosis
- Factors with marginal associations ($p<0.1$) in univariate analyses were included in multivariate models
- Each antiretroviral was included in the best-fitting multivariate model to assess the effect of its exposure on the subsequent risk of either bone outcome.
- Secondary analyses restricted to osteoporotic fractures (grouped as fractures of the spine, arm, wrist and hip)

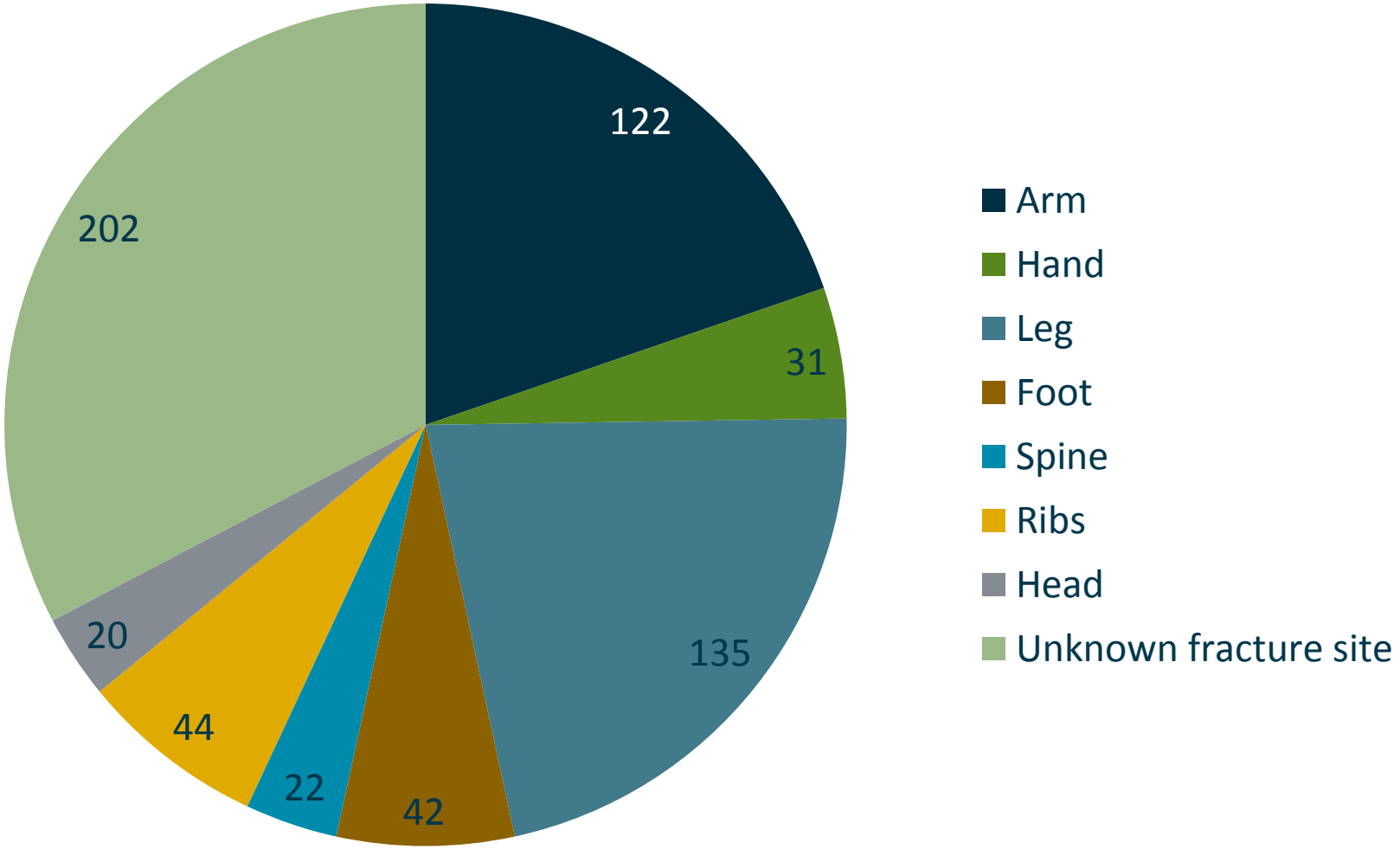
Results: Inclusion of participants



Baseline: latest of 1 January 2004 and recruitment to EuroSIDA. Baseline CD4/VL defined as last measurement before baseline (and within 6 months) or if none before, first after baseline (and within 6 months).

*Includes persons enrolled into Cohort 10 with only baseline data

Fracture sites (N=619): broad categories



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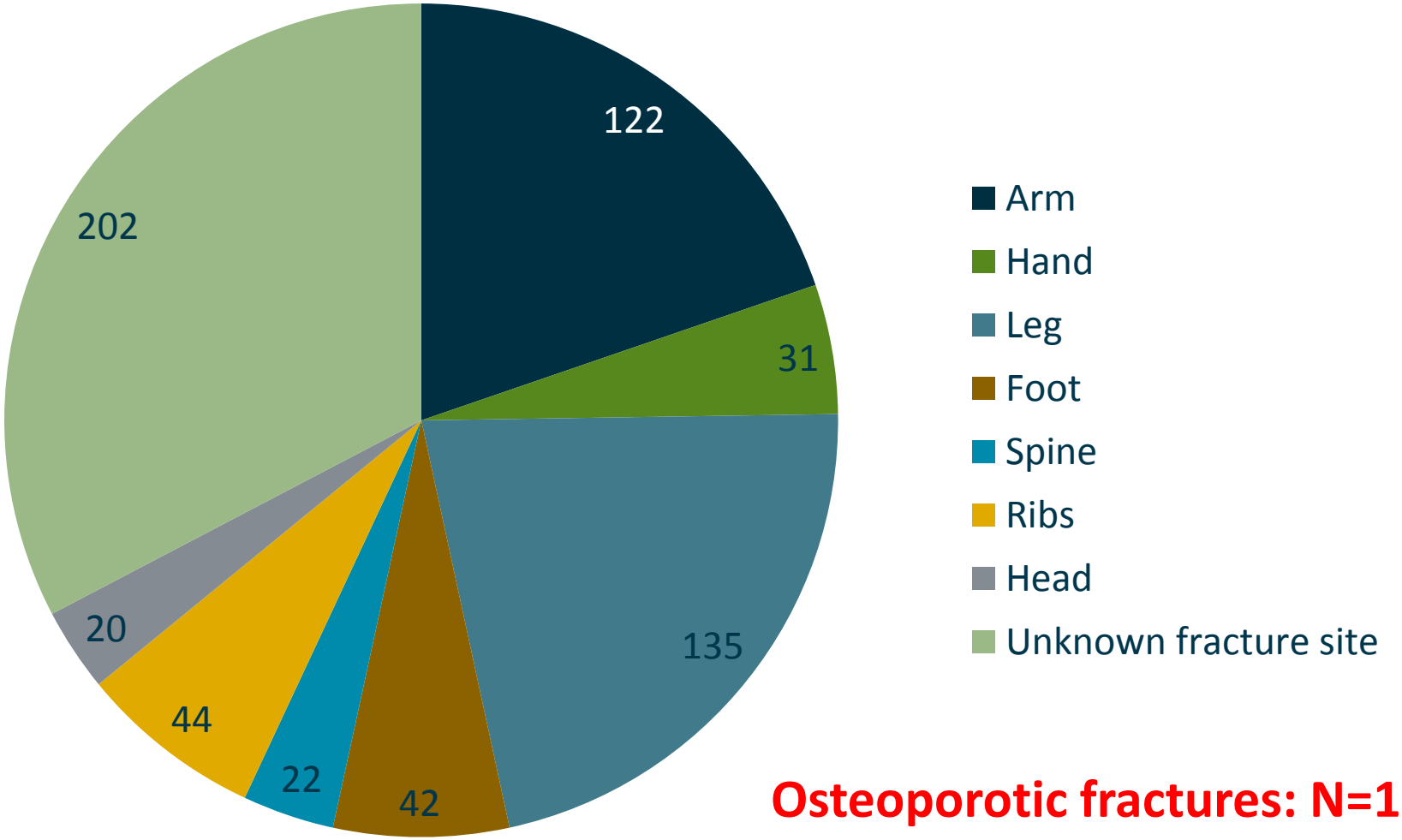
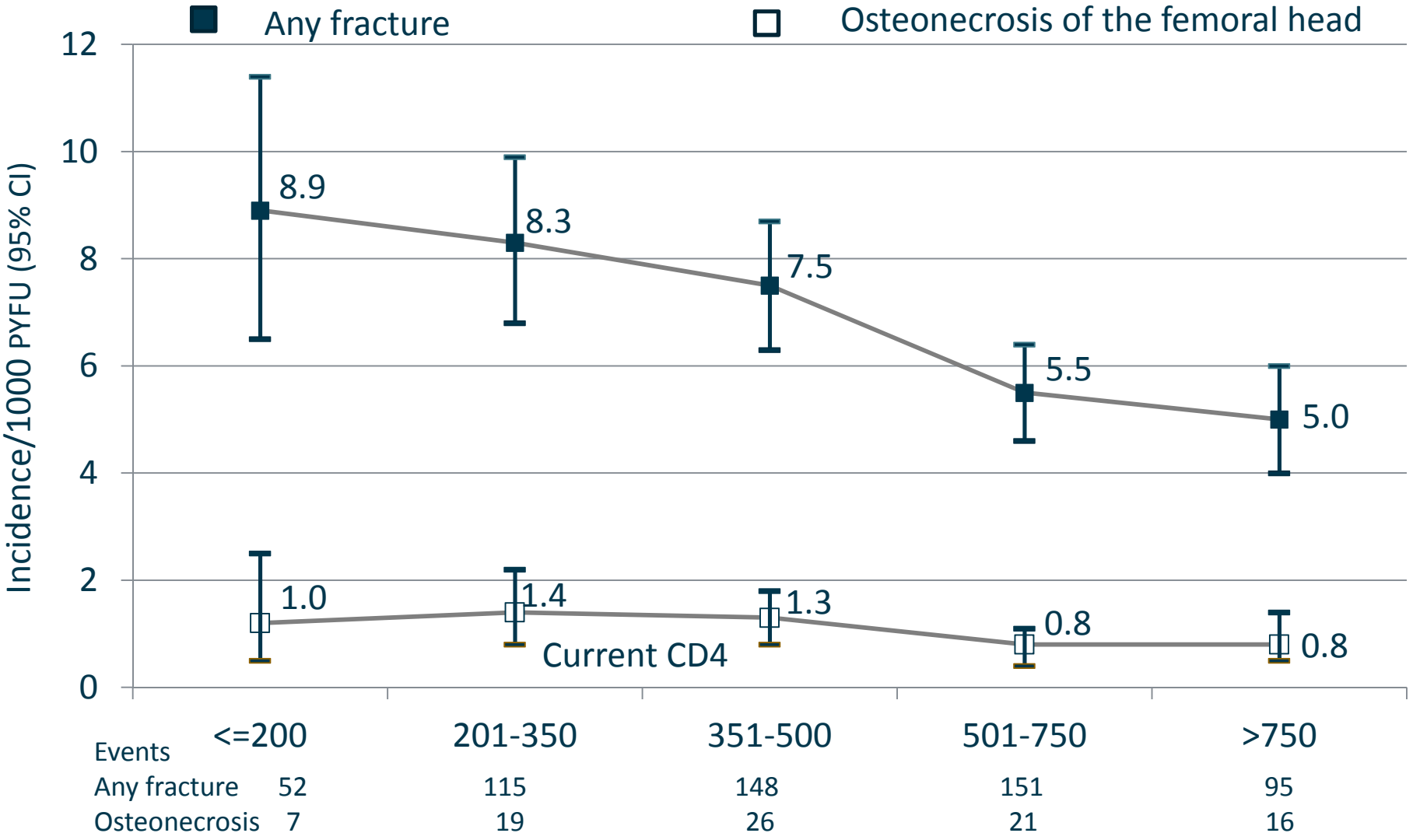


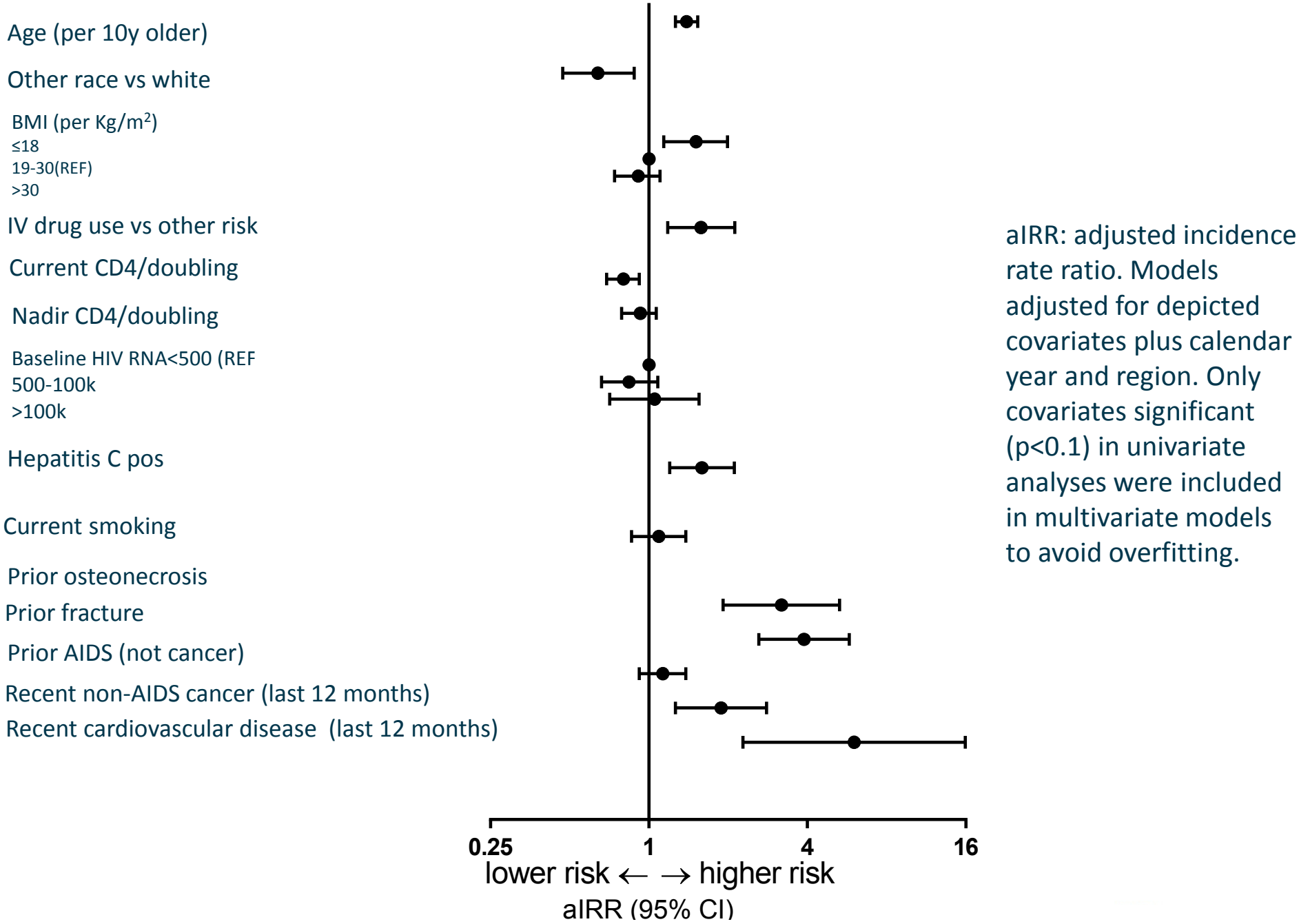
Osteoporotic fractures: N=132

Results: Incidence of new fractures and osteonecrosis

Stratified by current CD4

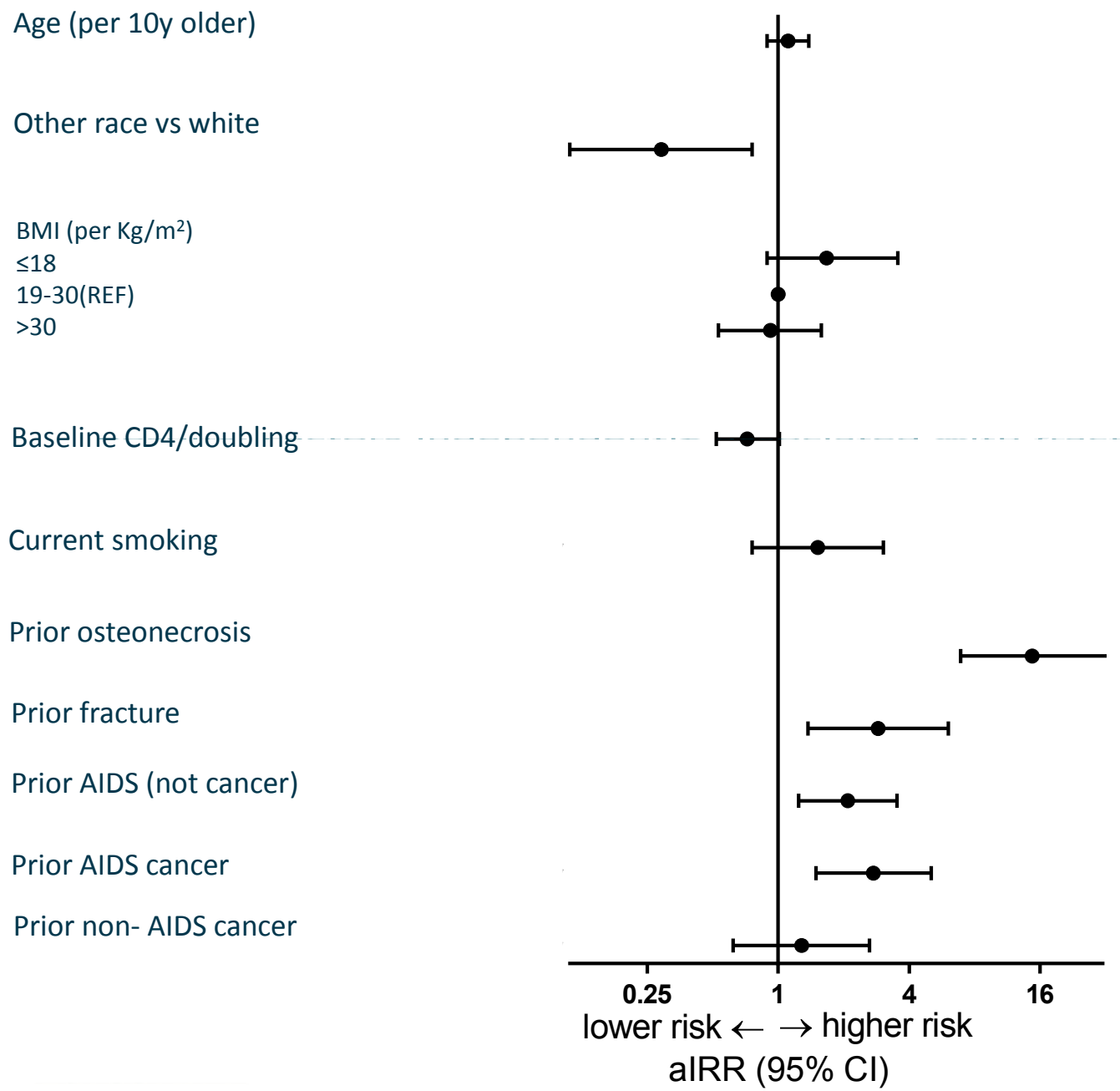


Results: Factors independently associated with fractures (N=619)



aIRR: adjusted incidence rate ratio. Models adjusted for depicted covariates plus calendar year and region. Only covariates significant ($p<0.1$) in univariate analyses were included in multivariate models to avoid overfitting.

Results: Factors independently associated with osteonecrosis (N=89)



aIRR: adjusted incidence rate ratio. Models adjusted for depicted covariates plus calendar year and region. Only covariates significant ($p<0.1$) in univariate analyses were included in multivariate models to avoid overfitting.

Results: Characteristics at last visit for those with no bone event, or at last diagnosis of fracture or osteonecrosis

Co-morbidities N(%)/ Median (IQR)	No bone event	Fractures	Osteonecrosis	P value *
Overall	11266 (95.2)	496 (4.2)	73 (0.6)	
Chronic kidney disease [a]	583 (5.3)	26 (5.6)	5 (7.5)	0.71
eGFR [b] mL/min/1.73 m^2	95 (80,106)	96 (79,106)	94 (75,106)	0.58
Vitamin D [c] ng/ml	37 (22,65)	35 (15,83)	31 (9,40)	0.26

(a) CKD chronic kidney disease at any time before last visit or event date; defined as confirmed (> 3 months apart) eGFR < 60 for those with first eGFR > 60, or 25% decline where baseline eGFR< 60. eGFRs were calculated using CKD-EPI formula.

(b) eGFR was available for 11536 (97.5%); 11003 (97.7%) for those with no events, 466 (94.1%) for those with any fracture and 67 (91.8%) for those with femoral necrosis (p<0.0001).

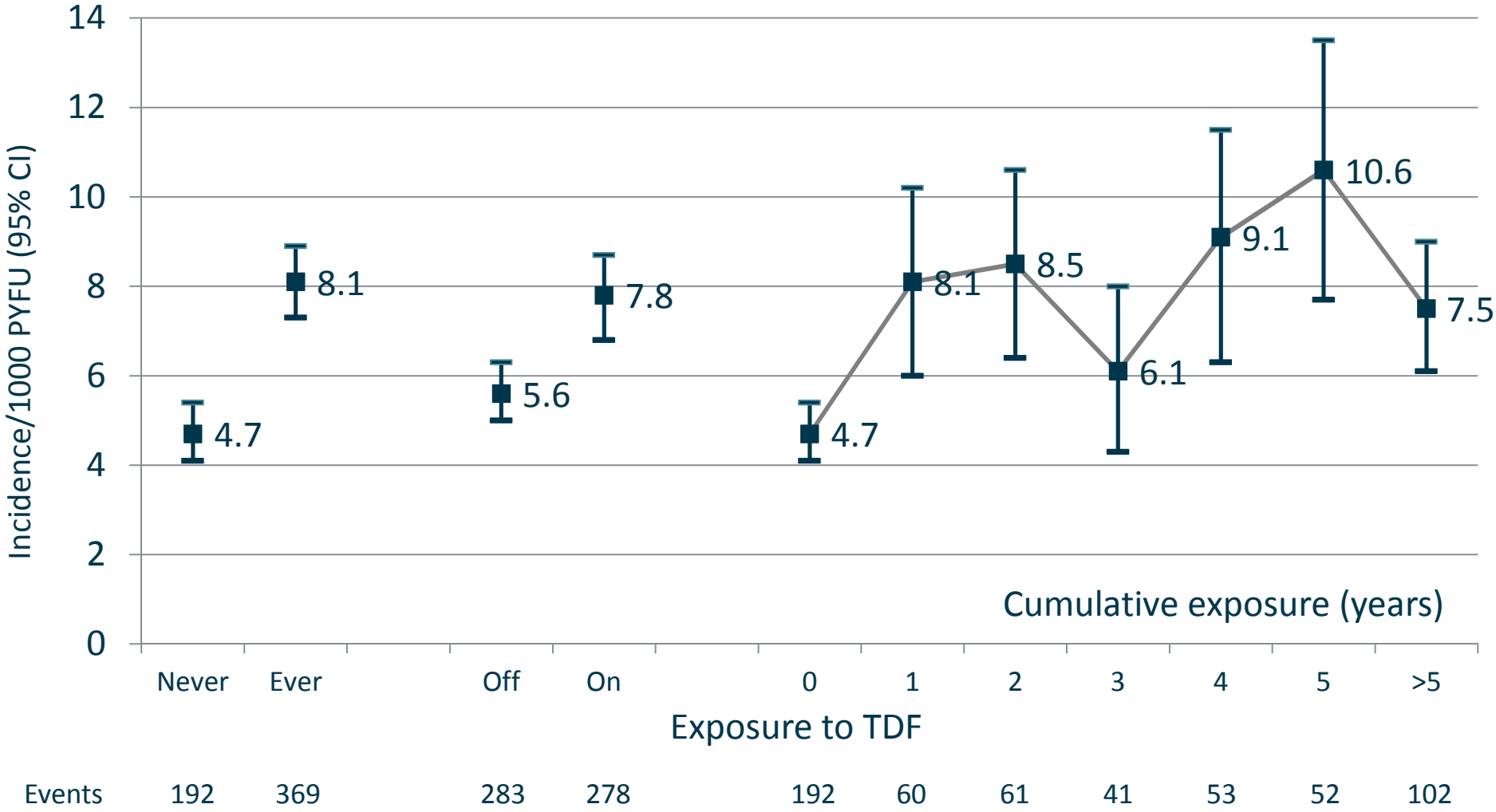
(c) Data available for 3291 (27.8%) overall, 3210 (28.5%) for those with no events, 71 (14.3%) for those with fractures and 10 (13.7%) of those with femoral necrosis (p<0.0001).

*global p-values for comparing across the three groups

Results

Crude incidence of new fractures

TDF use



Results: Effect of TDF exposure on fracture risk

TDF exposure	Any Fractures IRR (95% CI)		Osteoporotic fractures [a] IRR (95% CI)
	Univariate	Multivariate [b]	Multivariate [b]
Ever vs never TDF	**1.71** (1.42-2.06)	**1.40** (1.15-1.70)	1.10 (0.76-1.58)
On vs off TDF	**1.38** (1.16-1.64)	**1.25** (1.15-1.70)	1.12 (0.79-1.60)
Cumulative TDF exposure/ 5 years	**1.28** (1.13-1.50)	1.08 (0.94-1.25)	0.99 (0.69-1.43)

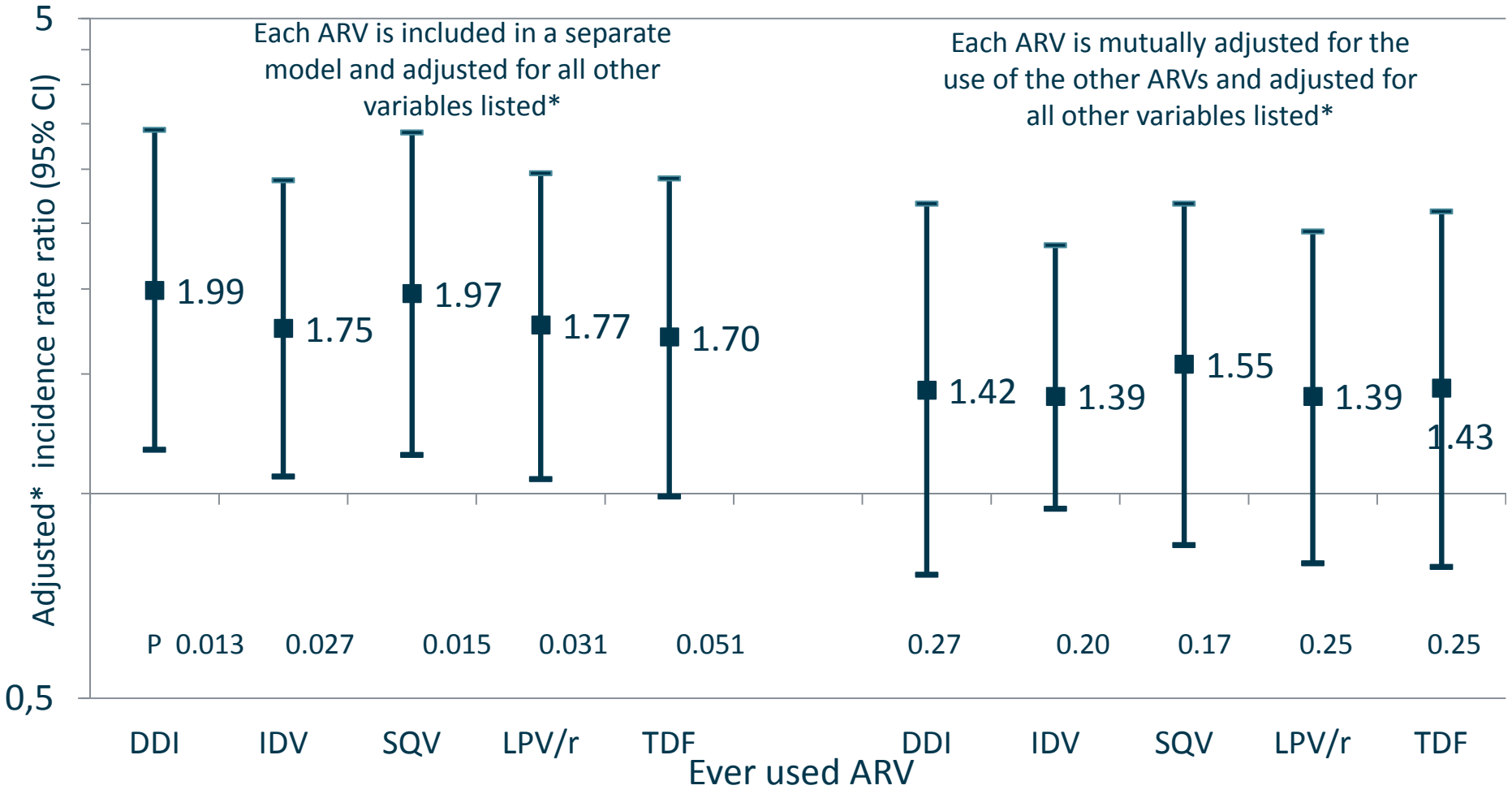
IRR: incidence rate ratio. **P< 0.05 for IRR (95% CI) written with bold letters**

[a] grouped as fractures of the spine, arm, wrist and hip

[b] adjusted for demographics, HIV-specific variables and co-morbidities

Results

Relationship between antiretroviral drugs and osteonecrosis



*adjusted for race, prior femoral necrosis at baseline, fracture⁺, age, nadir CD4 count, diagnosis of an AIDS defining malignancy⁺, non-malignant AIDS event⁺ and non-AIDS defining malignancy⁺

⁺time-updated variables

Conclusions

- Host factors, HIV-specific variables and co-morbidities contribute to risk of fractures and osteonecrosis in people living with HIV.

- Current or past exposure to TDF, but no other antiretroviral, was independently associated with higher incidence of any fracture. Similar results were seen in those with osteoporotic fractures.

- Persons who had ever used didanosine, indinavir, saquinavir, lopinavir/r, or TDF had higher risk of osteonecrosis, but this association was no longer significant after mutual adjustment.

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Funding:

Primary funding for EuroSIDA is provided by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n° 260694. Current support also includes unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).