Incidence of CKD With TDF and Non-TDF Containing Antiretroviral Regimens by Baseline D:A:D CKD Risk In People Living With HIV

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Disclosure

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Background

ART and chronic kidney disease (CKD)

- Established association between TDF use and risk of renal impairment
  - EuroSIDA (Mocroft 2010) , Veterans Health Administration (Scherzer 2012), D:A:D (Ryom 2013)

- Role of boosting agents exacerbating TDF toxicity
  - Meta-analysis of RCTs (Hill 2018)
  - Renal adverse events was not different between un-boosted TDF-regimens compared to TAF

- D:A:D CKD risk score
  - Developed in the D:A:D cohort and validated in European cohorts and in OPERA
  - Points allocated based on patient characteristics (IDU, HCV, age, eGFR, sex, nadir CD4, hypertension, CVD, diabetes)
  - CKD baseline risk categorized on D:A:D definitions (<0: Low, 0-4: Medium, 5+: High)

Objectives

Primary objective:

To assess the risk of incident CKD associated with TDF vs. non-TDF ART stratified by baseline D:A:D CKD risk score

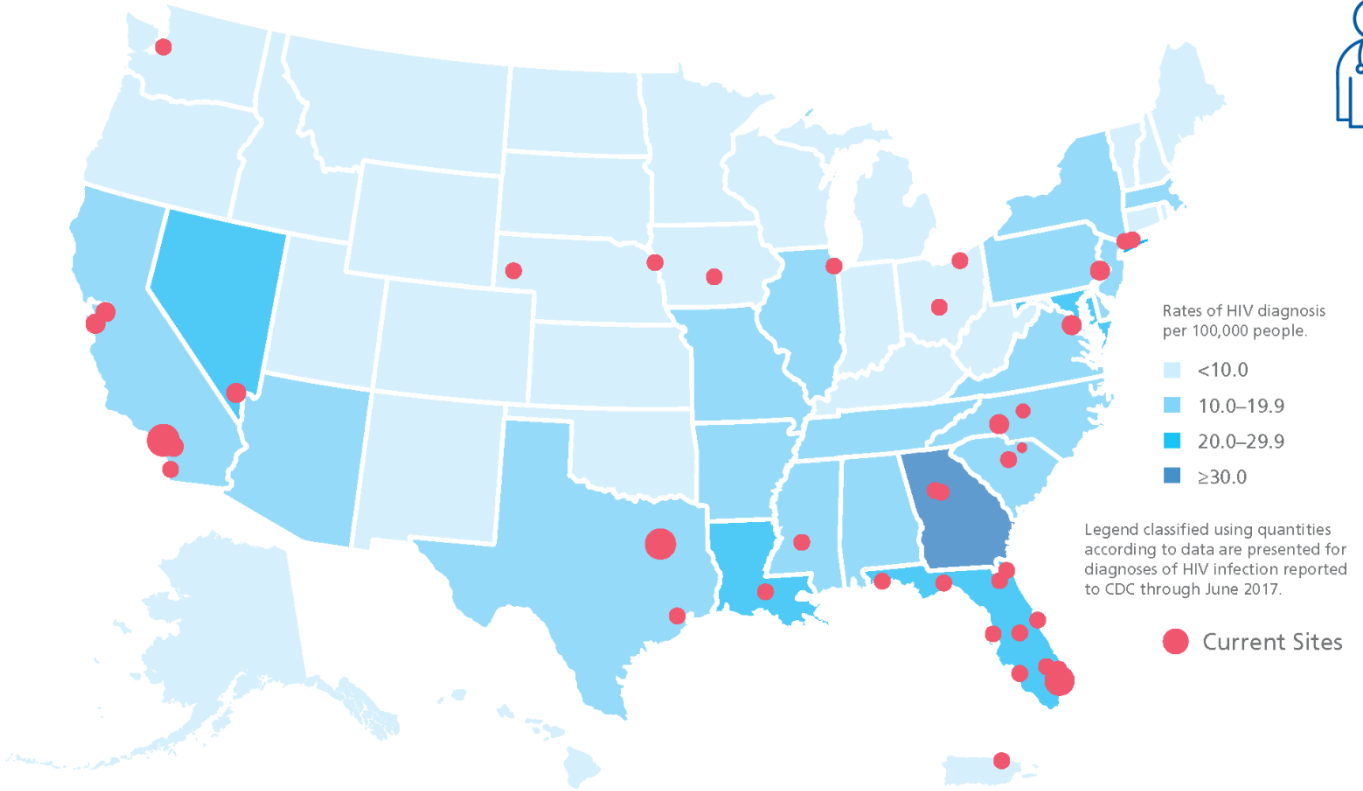
Secondary objective:

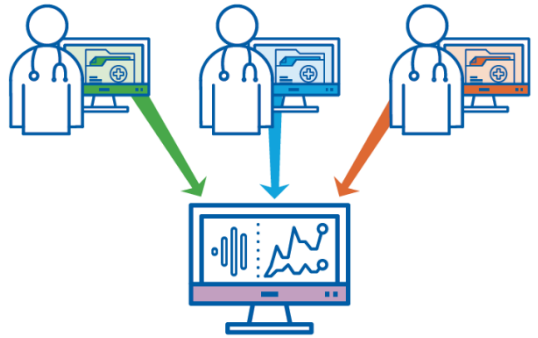
To assess the contribution of boosting agents on incident CKD risk

Methods

OPERA Cohort

- Prospectively captured, routine clinical data from electronic health records
- 100,000+ PLWH, 65 cities, 19 States, 1 US Territory





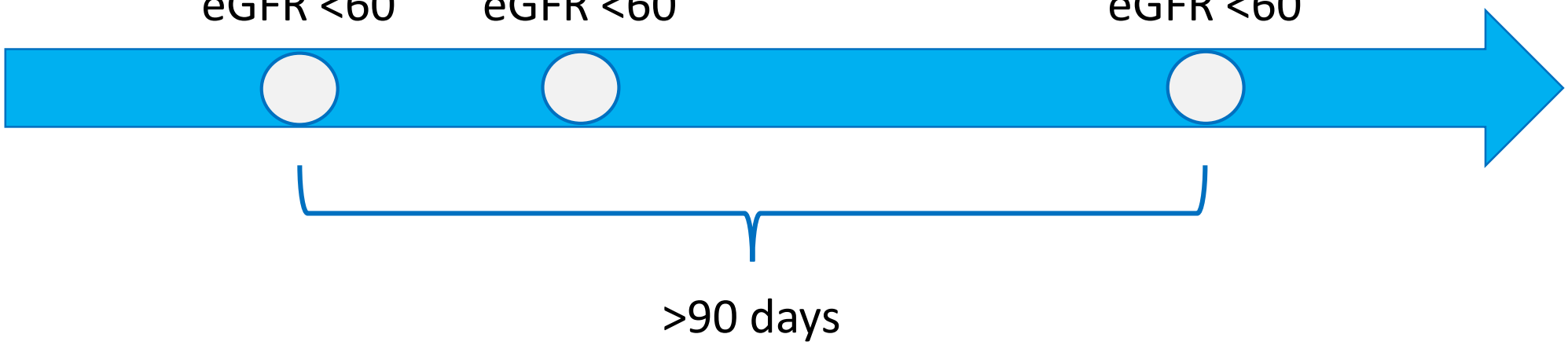
~ 8%
of all PLWH receiving care in the US

Study Population

- ART-naïve adults initiating ART by 30JUN2018
- ≥1 eGFR ≥ 60 ml/min/1.73m^2 within 12 months before initiation
- No dialysis, kidney transplant, end-stage liver disease, sepsis, or uncontrolled diabetes (2 consecutive HbA1c ≥6.5%)
- ≥2 eGFR measures after ART initiation
- PLWH with missing race/ethnicity excluded from statistical models

Incident CKD Assessment

- eGFR calculated with CKD-EPI equation
- ≥2 consecutive eGFR <60 ml/min/1.73m^2, >90 days apart



Statistical Analyses

- Incidence rates: Poisson regression
- Survival analysis: Pooled logistic regression
  - Generalized estimating equations (GEE), autoregressive correlation structure
  - Adjusted for:

Baseline:
Age
Sex
Race/ethnicity
Calendar year
Boosting/anchor class

Time-updated:
HIV VL <50 copies/mL
Nephrotoxic meds
Meds affecting proteinuria
Alcohol abuse
HCV
Diabetes
Hypertension

Sensitivity Analysis

- Some ARVs inhibit tubular creatinine secretion which leads to artificially low eGFR

- Correction of eGFR based on average decrease in clinical trials

	Average eGFR decrease in RCTs	Correction factor
DTG [1-4]	-16.5	eGFR + 17
EVG/c [5-8]	-14.2	eGFR + 14
PI/c [9]	-10.9	eGFR + 11
RAL [1,2,10]	-8.6	eGFR + 9
RPV [11,12]	-8.3	eGFR + 8

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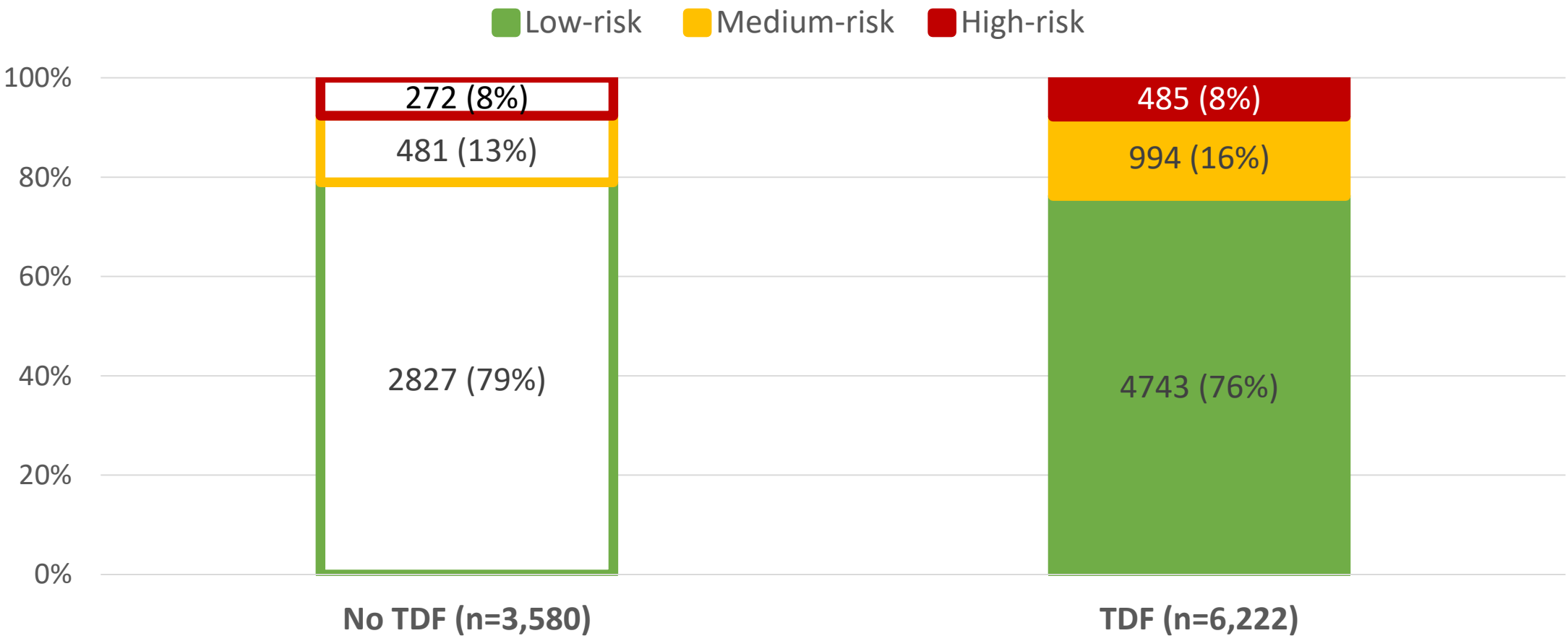
Results

Primary objective

OPERA®
The Longitudinal Cohort

Study Population (N = 9,802)



Median follow-up (IQR):	19 months (13-28)	29 months (18-45)

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Baseline Demographic Characteristics

	No TDF			TDF		
D:A:D CKD risk strata	**Low-risk N= 2,827**	**Medium-risk N= 481**	**High-risk N= 272**	**Low-risk N= 4,743**	**Medium-risk N= 994**	**High-risk N= 485**
Age	29 (25, 35)	49 (41, 53)*	52 (47, 57)*	31 (26, 38)*	48 (41, 53)*	52 (46, 57)*
Female	254 (9%)	97 (20%)*	79 (29%)*	566 (12%)*	174 (18%)*	146 (30%)*
Race/ethnicity		*	*	*	*	*
Black non-Hispanic	1334 (47%)	205 (43%)	140 (52%)	2004 (42%)	337 (34%)	183 (38%)
Other non-Hispanic	623 (22%)	154 (33%)	84 (31%)	1283 (27%)	435 (44%)	204 (42%)
Hispanic	775 (27%)	98 (20%)	37 (14%)	1283 (27%)	171 (17%)	66 (14%)
Missing	95 (3%)	24 (5%)	11 (4%)	173 (4%)	51 (5%)	32 (7%)
Year of ART initiation	2017 (2016, 2017)	2016 (2015, 2017)*	2016 (2014, 2017)*	2013 (2011, 2014)*	2012 (2010, 2014)*	2012 (2010, 2014)*

* All $p < 0.0001$ for the comparison with Low-Risk, No TDF

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Baseline Clinical Characteristics

	No TDF			TDF		
D:A:D CKD risk strata	**Low-risk N= 2,827**	**Medium-risk N= 481**	**High-risk N= 272**	**Low-risk N= 4,743**	**Medium-risk N= 994**	**High-risk N= 485**
eGFR	118 (106, 128)	96 (85, 106)*	77 (69, 86)*	116 (105, 126)*	96 (85, 107)*	81 (73, 87)*
Alcohol abuse	51 (2%)	16 (3%)	6 (2%)	109 (2%)	42 (4%)*	10 (2%)
Log10 HIV viral load	4.7 (4.2, 5.1)	4.7 (4.1, 5.2)	4.8 (4.2, 5.3)*	4.7 (4.2, 5.1)	4.8 (4.2, 5.2)	4.6 (4.1, 5.0)
Nephrotoxic medication[a]	303 (11%)	82 (17%)*	47 (17%)*	838 (18%)	253 (25%)*	134 (28%)*
Medication minimizing proteinuria[b]	69 (2%)	68 (14%)*	57 (21%)*	159 (3%)	119 (12%)*	93 (19%)*
HCV co-infection	58 (2%)	44 (9%)*	29 (11%)*	112 (2%)	119 (12%)*	75 (16%)*
Diabetes	34 (1%)	49 (10%)*	40 (15%)*	34 (1%)	70 (7%)*	42 (9%)*
Hypertension	561 (20%)	202 (42%)*	157 (58%)*	1074 (23%)	383 (39%)*	252 (52%)*

* $p < 0.05$ for the comparison with Low-Risk, No TDF

[a] ATV/r, LPV/r, acyclovir, cidofovir, valacyclovir, ganciclovir, valganciclovir, dipyridamole, NSAID, probenecid

[b] Ace inhibitor, Angiotensin II receptor blocker

Unadjusted CKD Incidence by TDF/CKD Risk

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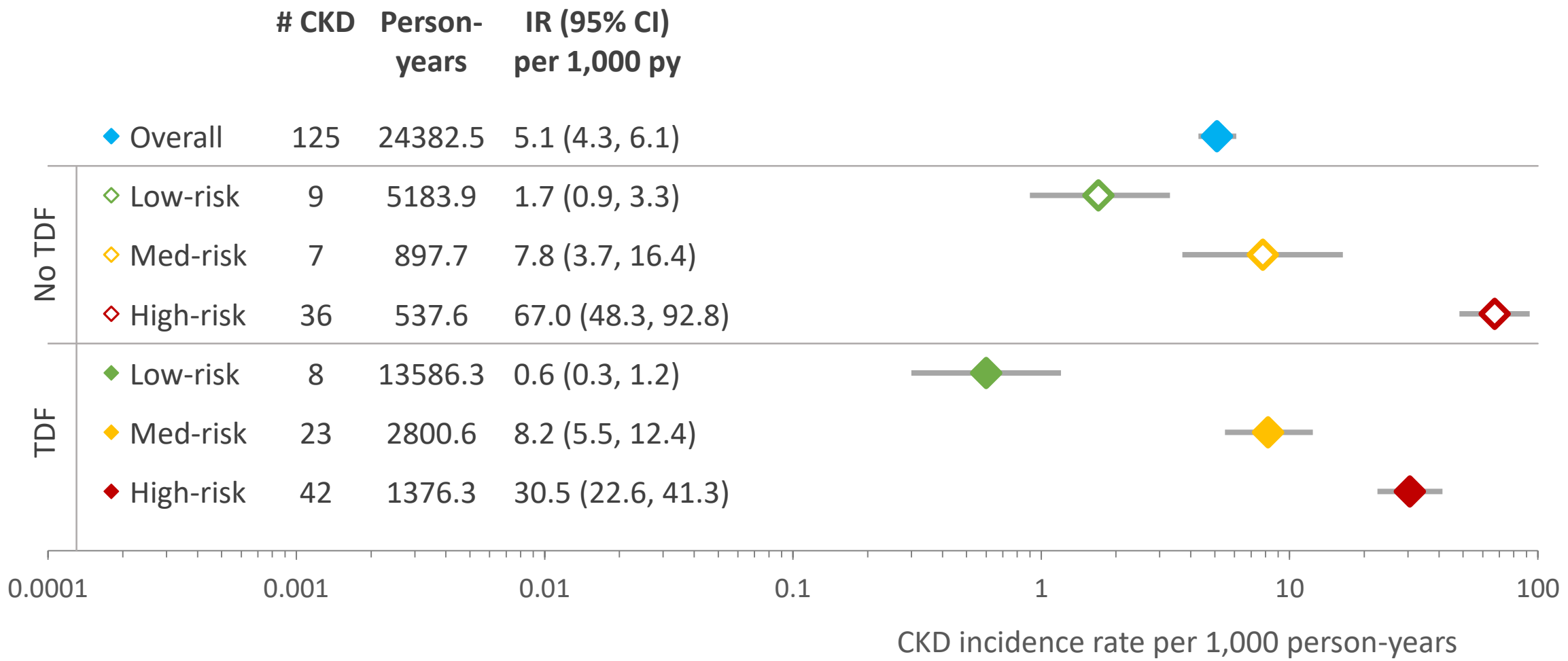

Unadjusted CKD Incidence by TDF/CKD Risk with eGFR correction

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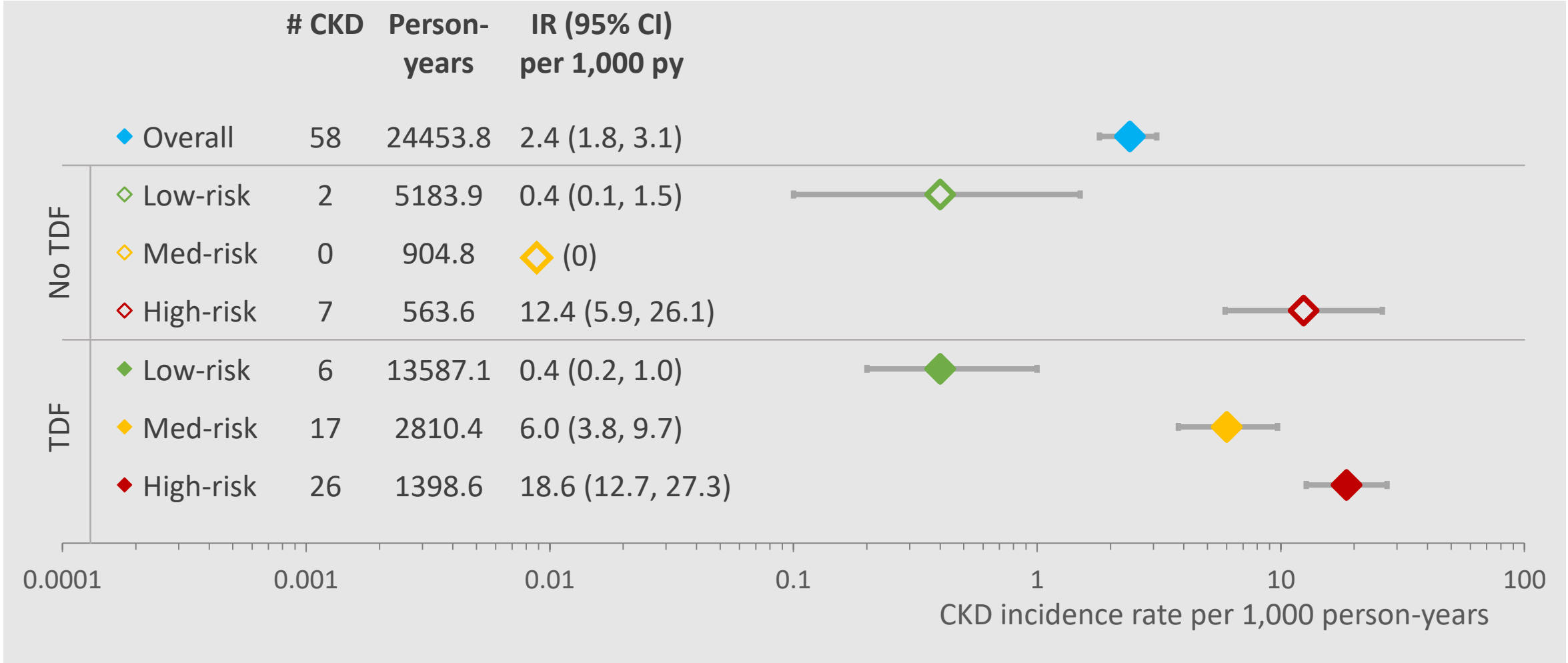
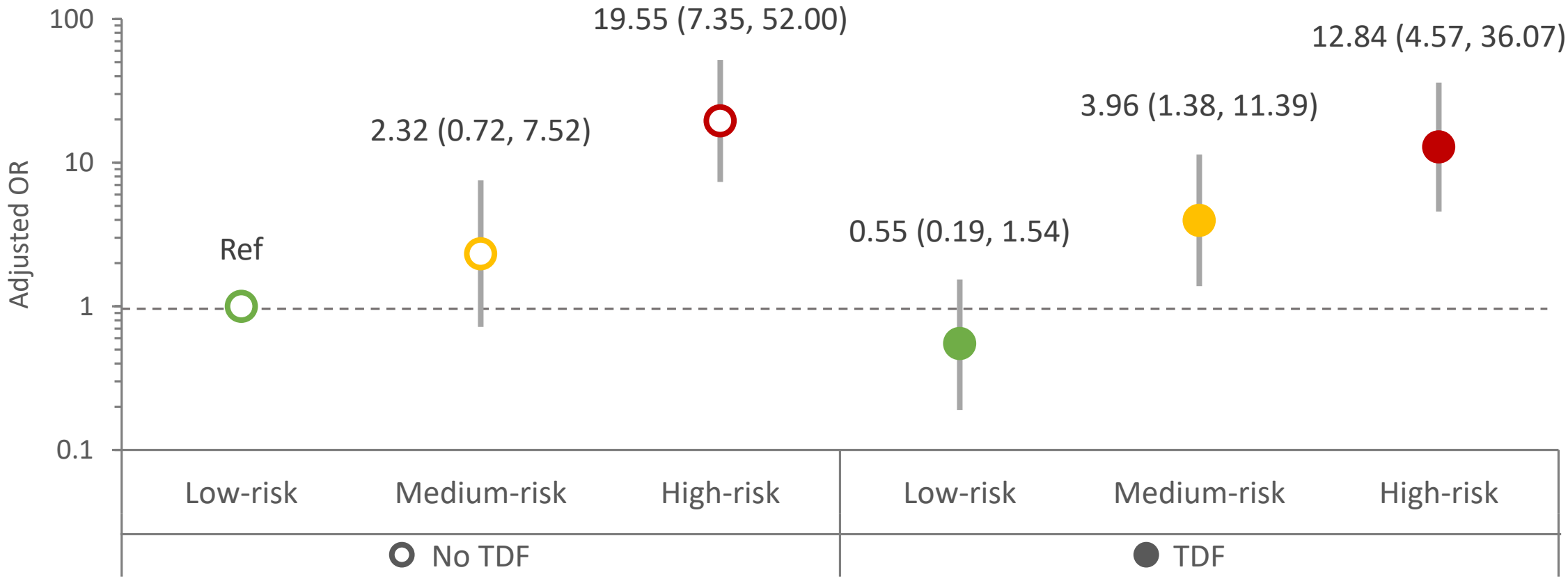


Adjusted* Association Between Incident CKD and TDF/Baseline CKD Risk



* Adjusted for baseline age, sex, race/ethnicity, calendar year & boosting/anchor class, and time-updated alcohol abuse, HIV viral load, medications (nephrotoxic, affecting proteinuria), HCV, diabetes & hypertension

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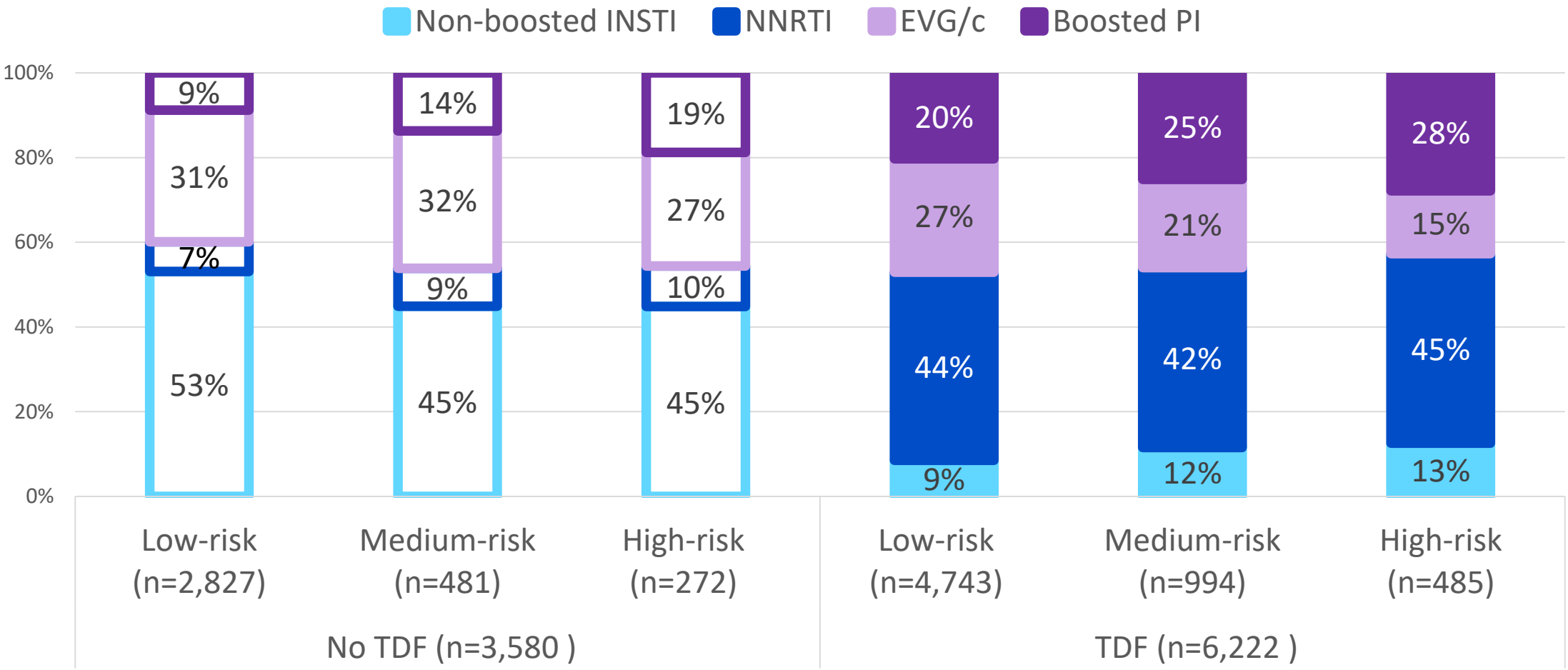
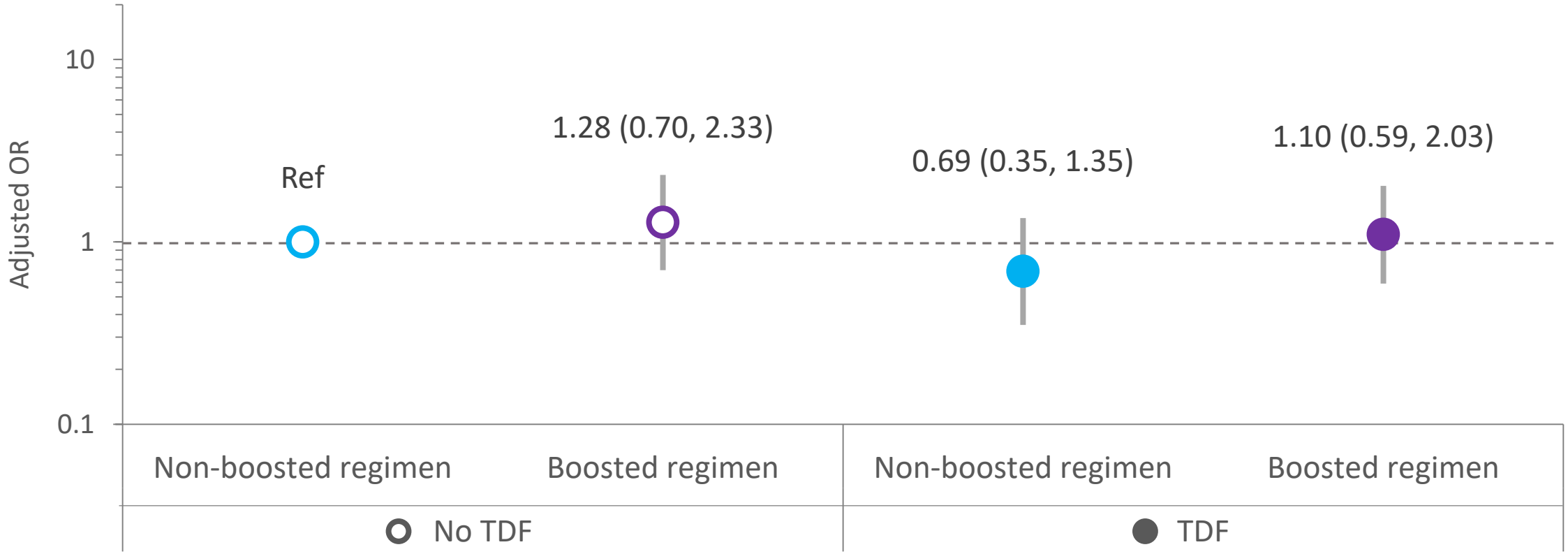
Study Population by TDF/Boosting

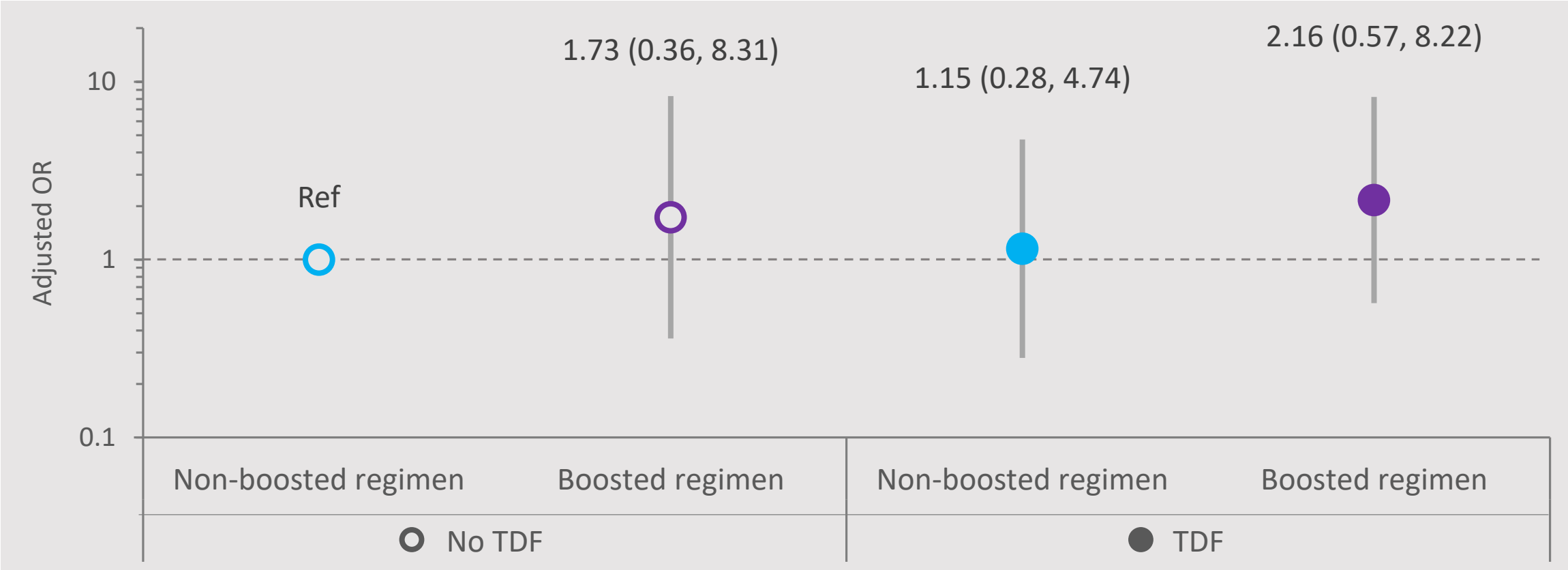


Adjusted* Association Between CKD and TDF/Boosting



* Adjusted for baseline age, sex, race/ethnicity, calendar year & D:A:D risk score, and time-updated alcohol misuse, HIV viral load, medications (nephrotoxic, affecting proteinuria), HCV, diabetes & hypertension

Adjusted* Association Between CKD and TDF/Boosting with eGFR correction



* Adjusted for baseline age, sex, race/ethnicity, calendar year & D:A:D risk score, and time-updated alcohol misuse, HIV viral load, medications (nephrotoxic, affecting proteinuria), HCV, diabetes & hypertension

Discussion

Key Findings (1)

- Low incidence of CKD after ART initiation in ART-naïve PLWH
- Progression to CKD strongly associated with baseline D:A:D CKD risk score
- Low baseline D:A:D CKD risk score
  - Largest group of ART-naïve PLWH (76-79%)
  - No increase in incident CKD risk with TDF in the low-risk D:A:D stratum
  - TDF may remain a viable option in PLWH with low CKD risk at initiation

Key Findings (2)

- No observed association between risk of CKD with TDF and boosted regimens

- eGFR correction
  - Reduced number of incident CKD events
  - Increased CKD incidence rates with TDF and with higher baseline D:A:D risk as expected
  - Trend towards higher risks of incident CKD with boosted regimens
  - No increase in incident CKD risk with TDF in the low-risk D:A:D stratum

Strengths

+ OPERA cohort
  - >100,000 PLWH
  - Database combining several different electronic medical records systems
  - Availability of lab results, diagnosis codes and care provider's notes

+ Large study population (N = 9,802)

+ Longer median follow-up with TDF (29 months) vs. without TDF (19 months): sufficient time to observe events in the exposed group

+ Adjusted for eGFR correction and time-updated confounders
  - Concurrent medications, incident comorbidities

Limitations

- Exclusion of PLWH missing race/ethnicity data

- Incident CKD was a rare outcome
  - Limited power to detect differences
  - Could not assess the role of ART class due to small number of events

- Limited number of CKD events after eGFR correction preventing statistical modeling

- Residual confounding
  - Confounding by indication, no adjustment for duration of CKD risk factors

https://bit.ly/2m2nSHU

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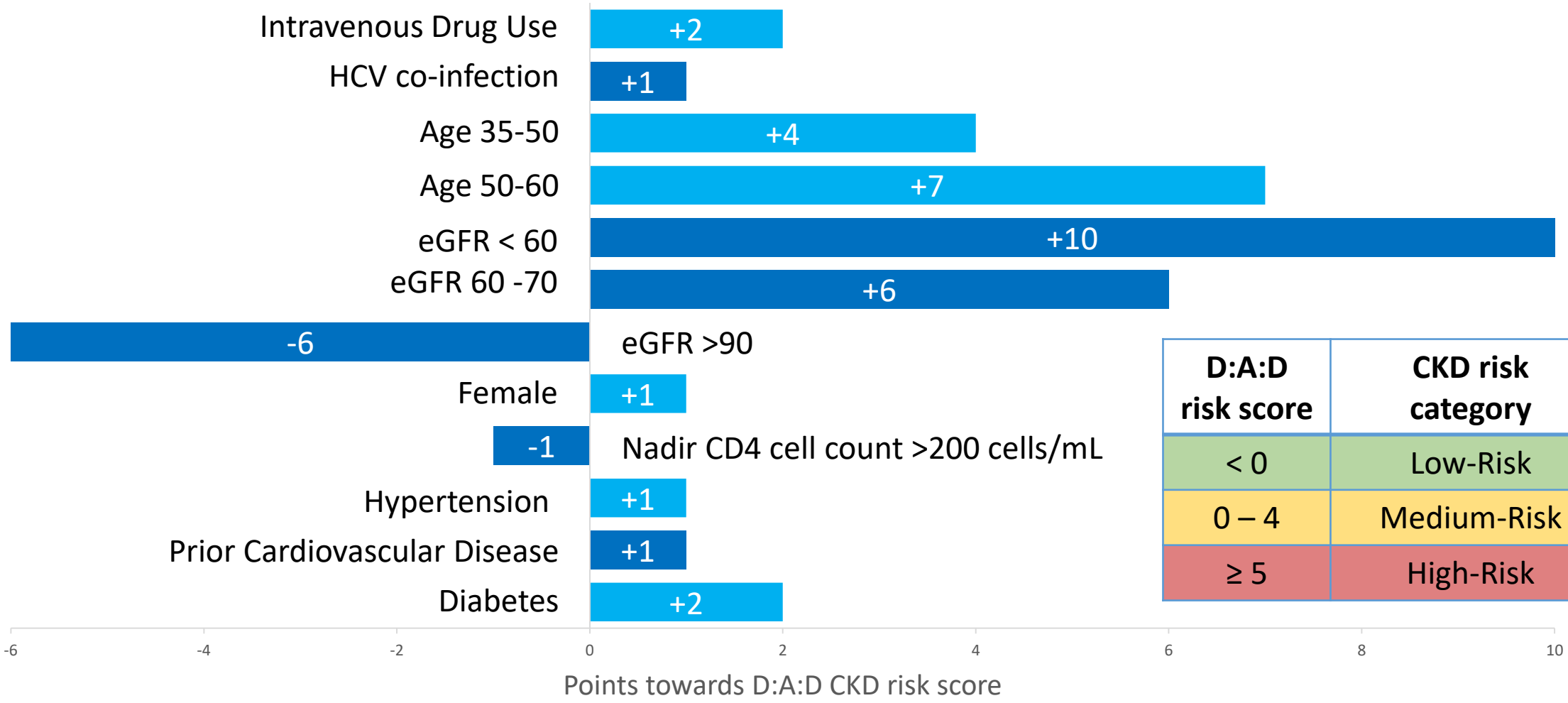
Additional slides

Study Population

Inclusion criteria	Included	Excluded
PLWH in OPERA	94,852	-
ART-naïve, initiating ART by June 30, 2018	21,356	73,496 (77%)
≥18 years old	21,298	58 (0%)
Initial regimen: 2 NRTIs + 1 anchor agent	18,262	3,036 (3%)
No kidney transplants	18,258	4 (0%)
No ESLD	18,243	15 (0%)
No dialysis within 12 months of initiation	18,233	10 (0%)
No uncontrolled diabetes within 8 months of initiation	18,193	40 (0%)
No sepsis within 3 months of initiation	18,182	11 (0%)
≥1 eGFR within 12 months of initiation	16,293	1,889 (2%)
Last eGFR prior to ART initiation is ≥60 ml/min/1.73m^2	16,043	250 (0%)
≥2 eGFRs after ART initiation, with >90 days between the first and last eGFR	**9,802**	6,241 (7%)

D:A:D CKD Risk Score



D:A:D risk score	CKD risk category
< 0	Low-Risk
0 – 4	Medium-Risk
≥ 5	High-Risk

Mocroft A, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med. 2015;12(3):e1001809.