CROI 2017, Seattle,
Late Breaker Presentation

# Association between Cardiovascular Disease & Contemporarily Used Protease Inhibitors

*L Ryom, JD Lundgren, W El-Sadr, P Reiss, A Phillips, O Kirk, R Weber, E Fontas, AD Monforte, S de Wit, F Dabis, CI Hatleberg, C Sabin, A Mocroft*
*On behalf of the D:A:D Study group*

chip Centre for Health & Infectious Disease Research

REGION H Rigshospitalet

Faculty of Health and Medical Sciences University of Copenhagen

D:A:D

# Background I

- Earlier studies, including prior D:A:D analyses, have demonstrated associations between cumulative use of first generation protease inhibitors (PIs) and cardiovascular disease (CVD)[1-3]

- The mechanism is believed to be partly mediated by dyslipidemia, and drugs within the PI drug class are associated with different metabolic profiles[4-9]

- It is unknown if more contemporarily used PIs in the current modern antiretroviral treatment era poses a similar risk of CVD as older PIs

1. N Engl J Med. 2007; 2. AIDS 2003; 3. Circ 2001; 4. Antivir Ther 2005;
5. CID 2004; 6. HIV Med 2005; 7. JID 2004; 8. Am J Cardio 2004; 9. J Clin Invest 2003

D:A:D

# Background II

- Presently, the two most frequently used PIs are ritonavir boosted darunavir (DRV/r) and atazanavir (ATV/r)[1]

- In a prior analysis from D:A:D, ATV/r was found not to be associated with excess CVD risk, however follow-up time was relatively short[2]

- With an ageing HIV-positive population with increasing underlying CVD risk due to higher number and severity of CVD risk factors it has become increasingly important to tailor antiretroviral treatment to the individual risk profile

1. HIV Med 2016; 2. AIDS 2013.

D:A:D

# Objectives

Is cumulative use of the contemporary PIs ATV/r and DRV/r independently associated with increased risk of CVD?

D:A:D

# Methods I

**Definitions**

CVD was defined, as in previous D:A:D analyses, as a composite endpoint including the following, centrally adjudicated, events:

- Myocardial infarction
- Stroke
- Sudden cardiac death
- Invasive cardiovascular procedures
  - Coronary bypass
  - Coronary angioplasty
  - Carotid endarterectomy

D:A:D

# Methods II

- D:A:D study participants under follow-up after Jan 1st 2009 (baseline) were followed to the earliest of CVD, last visit plus 6 months or Feb 1st 2016

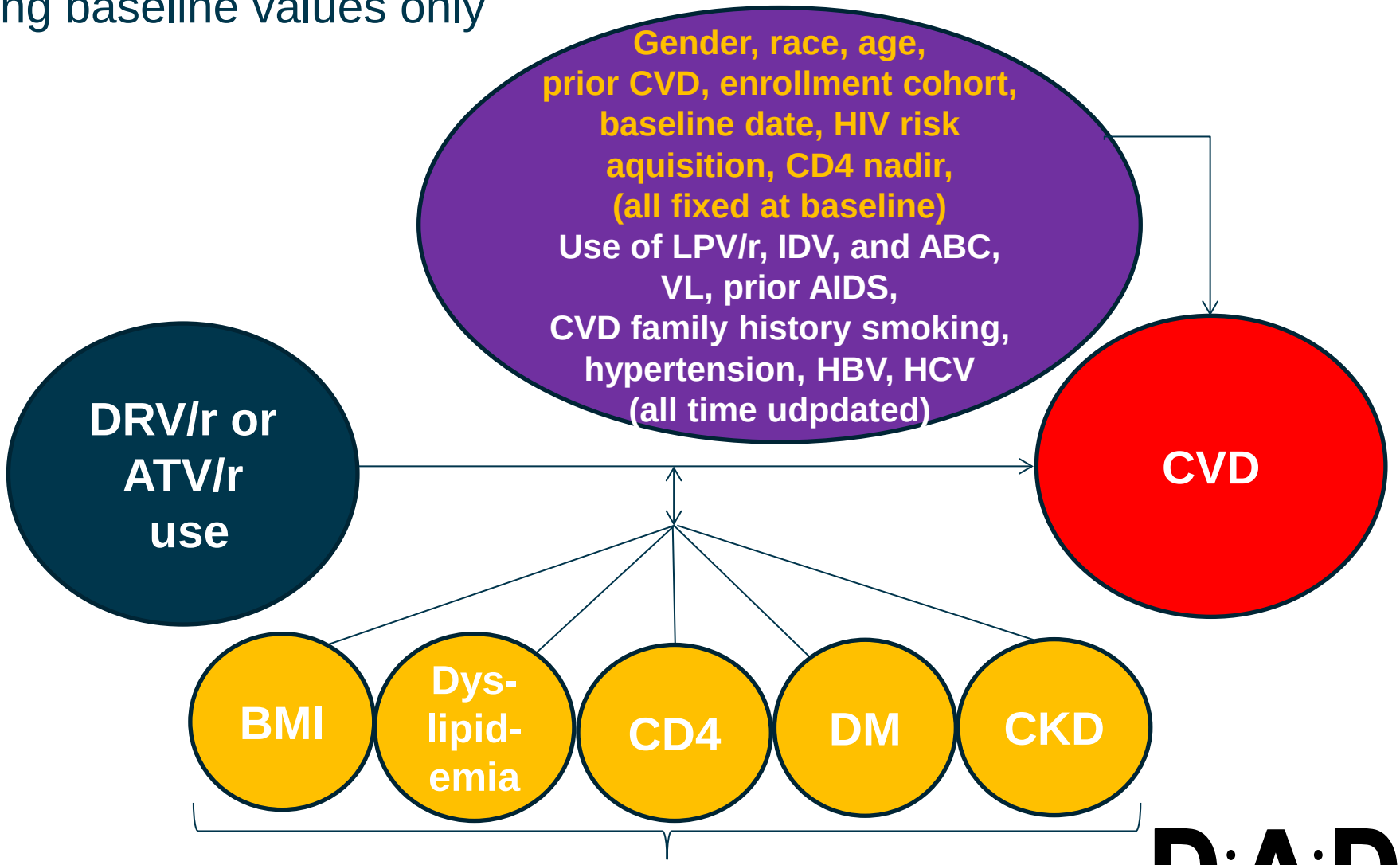
- CVD incidence rates were calculated and stratified by cumulative (per 5 year) exposure to ATV/r and DRV/r

- Poisson regression models were used to assess associations between CVD and use of ATV/r and DRV/r adjusting for potential confounders

D:A:D

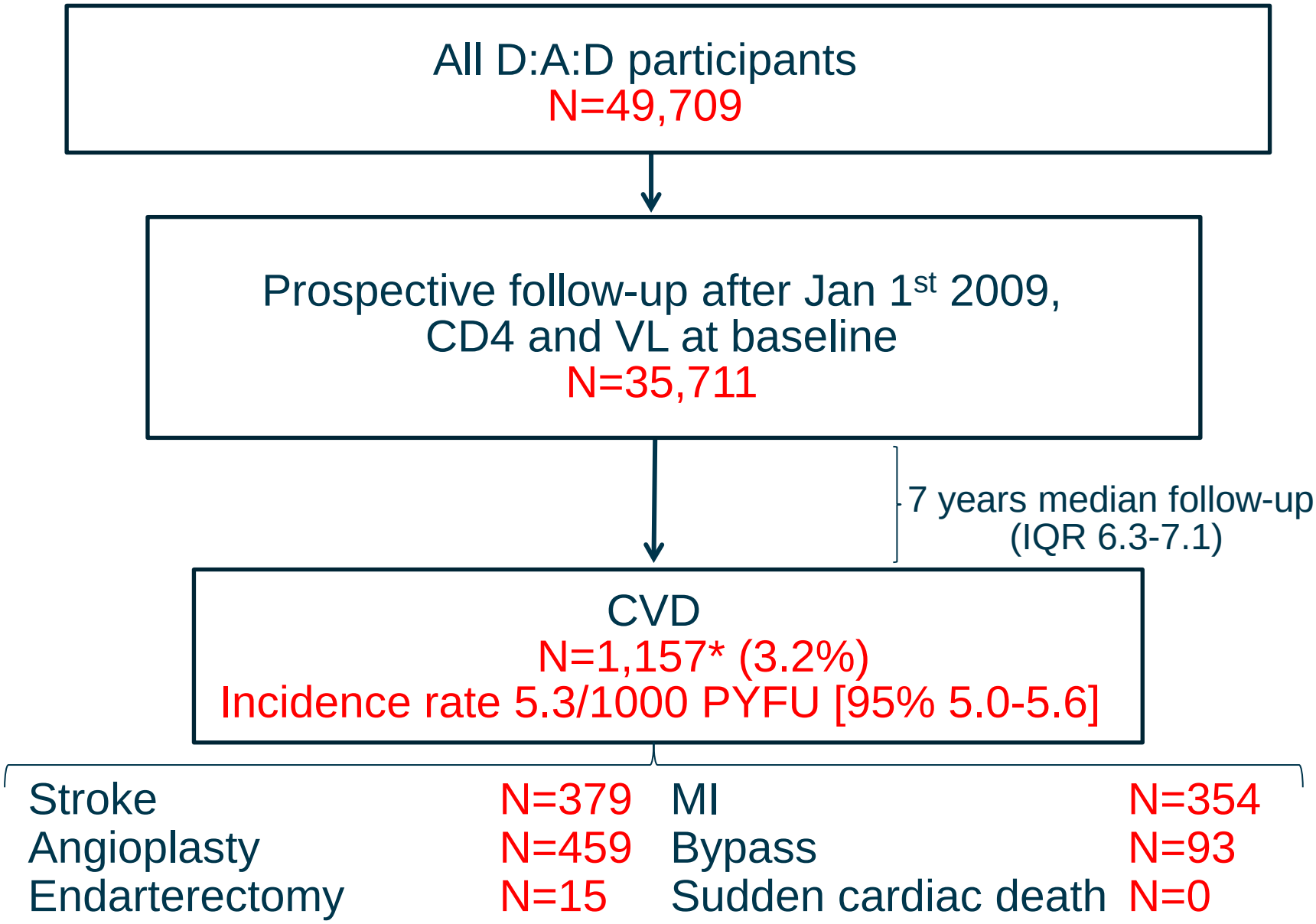
# Methods III

In the primary adjusted model, factors considered to potentially lie on the causal pathway between PI/r use and CVD were adjusted for using baseline values only




D:A:D

# Inclusion of D:A:D Participants into the Analysis

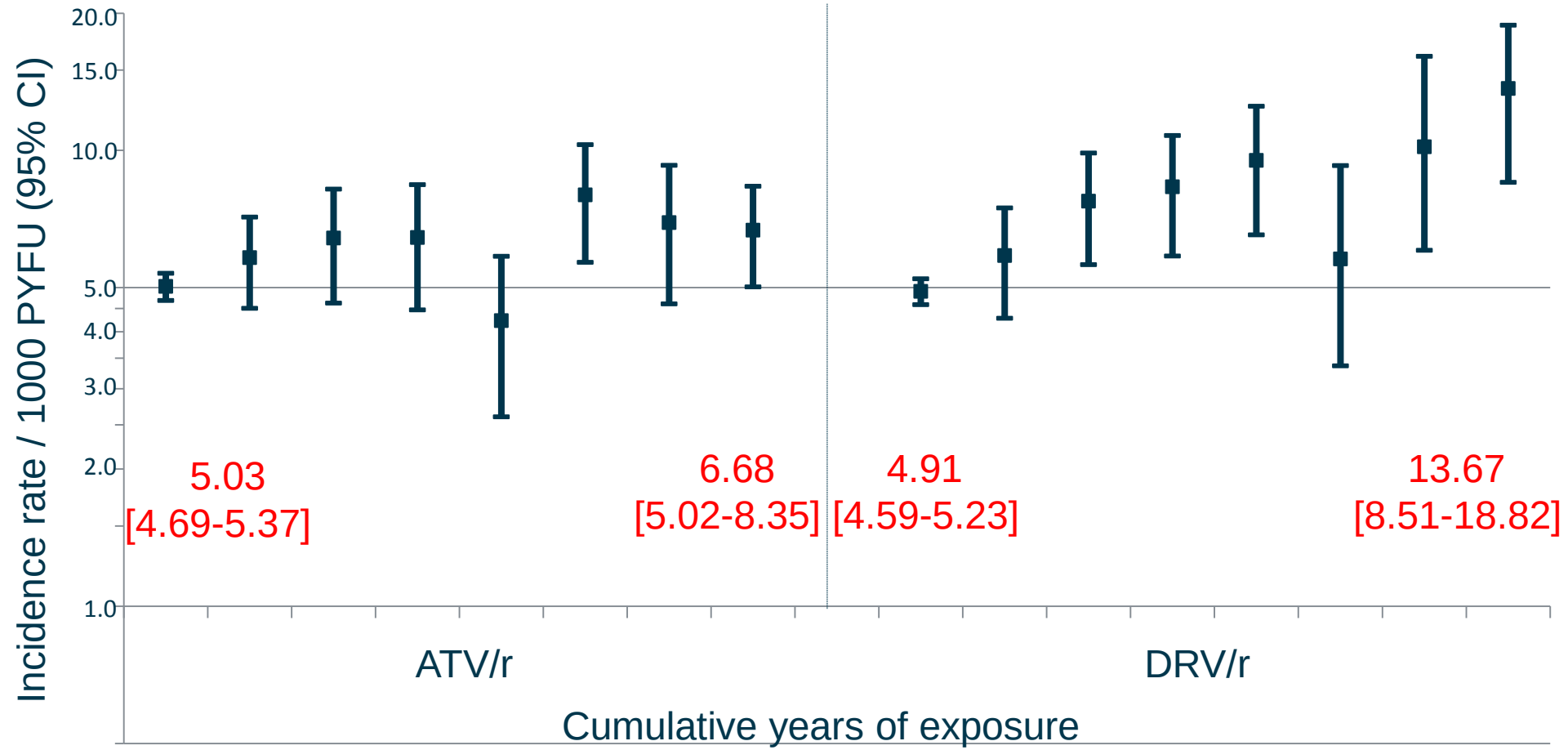



* Persons could experience multiple events on the same day

# Baseline Characteristics

| | | N | % |
|---|---|---|---|
| **All** | | 35711 | 100.0 |
| **Gender** | Male | 26288 | 73.6 |
| **Race** | White | 17085 | 47.8 |
| **HIV Exposure** | MSM | 16447 | 46.1 |
| **HCV** | Positive | 6864 | 19.2 |
| **HBV** | Positive | 1439 | 4.0 |
| **VL < 400 copies/mL** | Yes | 27290 | 76.4 |
| **Smoking** | Current | 14014 | 39.2 |
| **Diabetes** | | 1805 | 5.1 |
| **Hypertension** | | 3471 | 9.7 |
| **Dyslipidemia** | | 14347 | 40.2 |
| **Prior AIDS** | Yes | 9799 | 27.4 |
| **Prior CVD** | Yes | 8515 | 28.6 |
| **D:A:D CVD Risk** | >10% | 1753 | 5.3 |
| **D:A:D CKD Risk** | High (≥5) | 11952 | 38.4 |
| | | **Median** | **IQR** |
| **Age** | years | 44 | 38-44 |
| **CD4** | cells/mm$^3$ | 501 | 360-689 |
| **Nadir CD4** | cells/mm$^3$ | 210 | 100-322 |

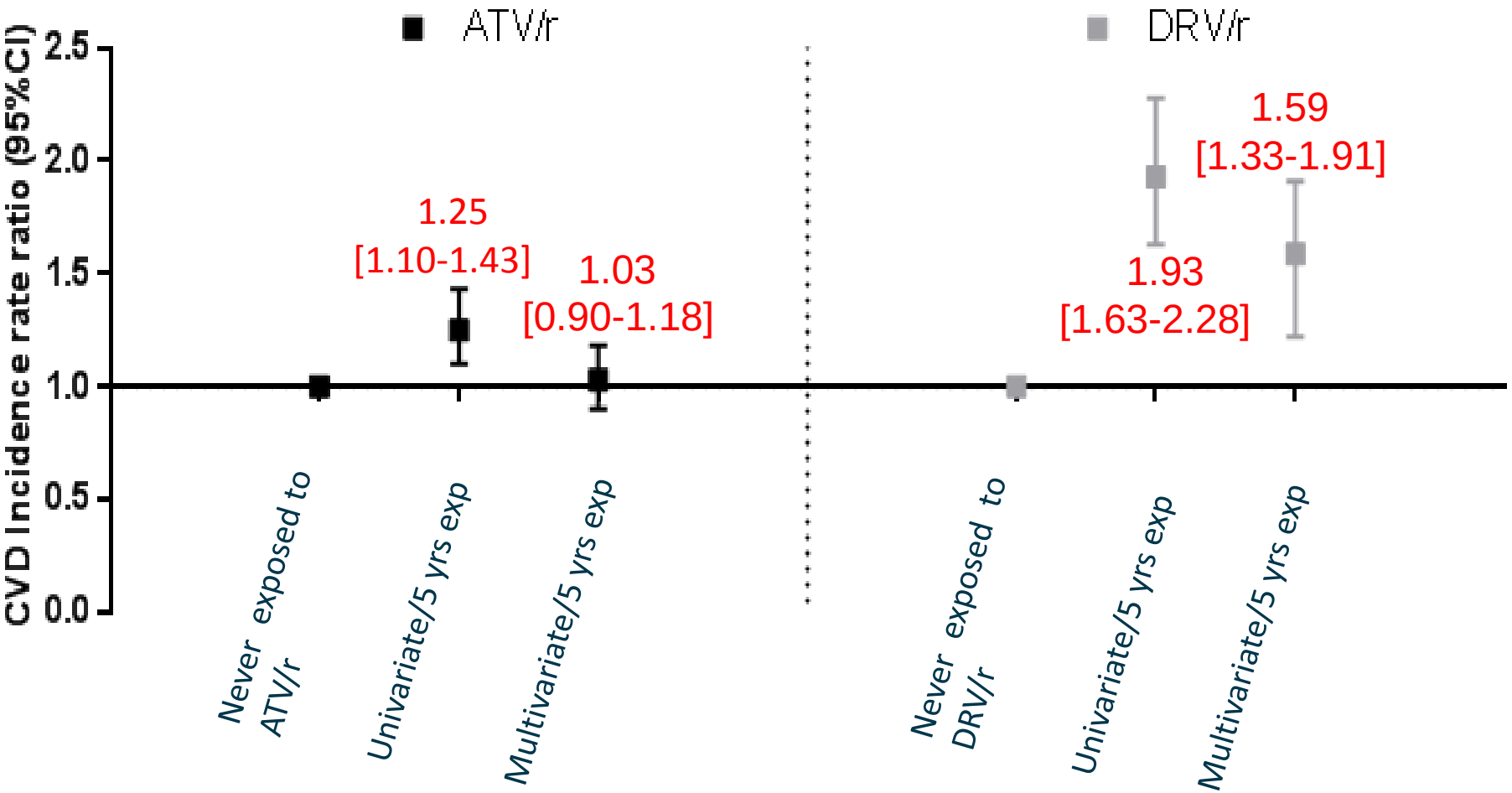
# Crude Incidence Rates of CVD per 1000 PYFU Stratified by Cumulative Use of ATV/r and DRV/r




| | 0 | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | >6 | 0 | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | >6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Events | 824 | 75 | 49 | 41 | 26 | 46 | 34 | 62 | 909 | 52 | 51 | 44 | 39 | 17 | 18 | 27 |
| PYFU | 163785 | 12886 | 7631 | 6369 | 6144 | 5757 | 4898 | 9278 | 185246 | 8845 | 6591 | 5285 | 4100 | 2940 | 1768 | 1975 |

# Association Between CVD & Cumulative ATV/r and DRV/r Use

## Primary Model; Baseline Adjustment Only for Variables Potentially on the Causal Pathway between PI/r Use and CVD

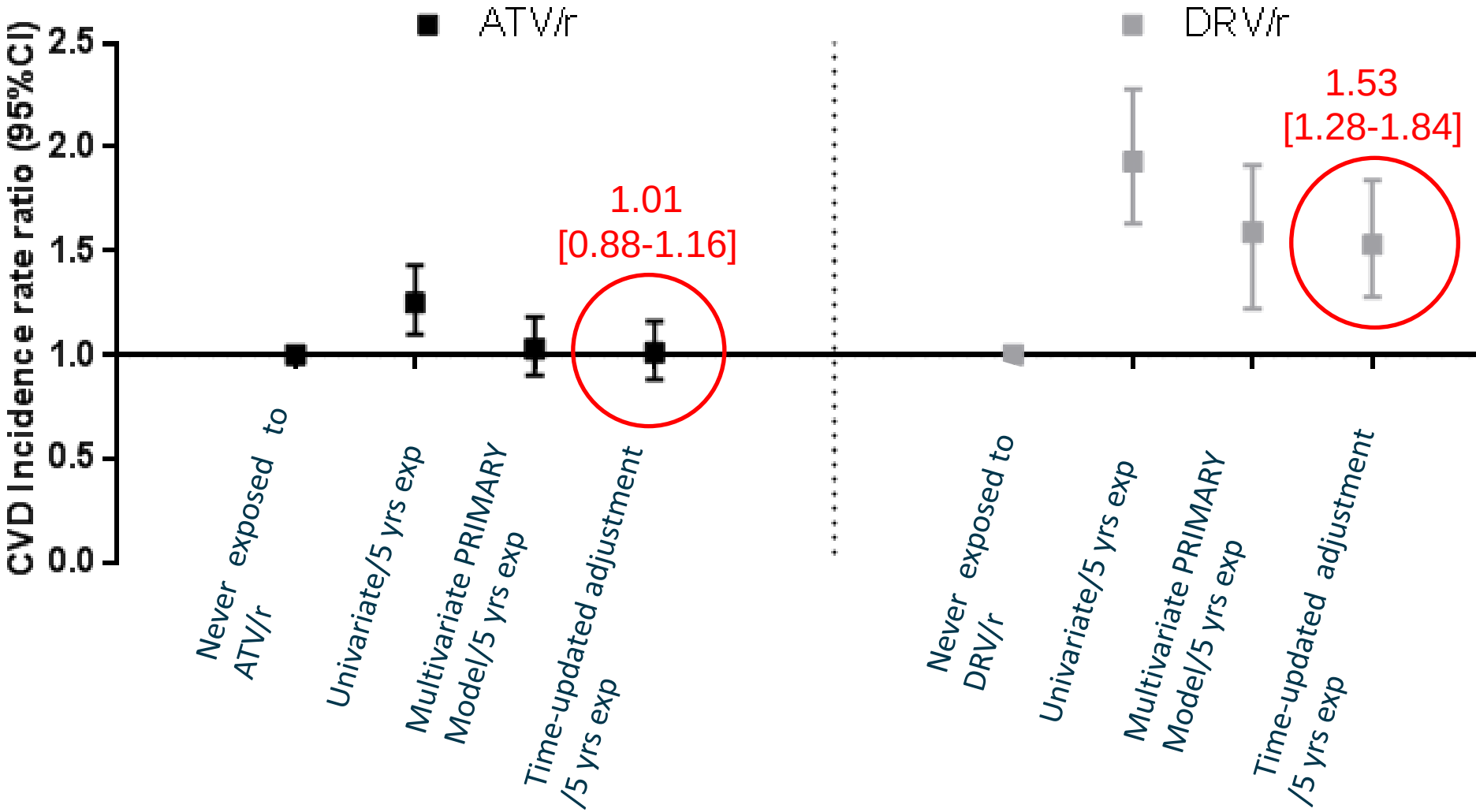



Multivariate models were adjusted for gender, age, race, HIV risk of aquisition, enrollement cohort, baseline date, prior CVD, CD4 nadir, CD4, BMI, diabetes, dyslipidamia, eGFR (all fixed at baseline), cumulative exposure to DRV/r, ATV/r, LPV/r and IDV, recent exposure ABC, prior AIDS, viral load, hepatitis B & C, family history of CVD, hypertension, smoking (all time updated)

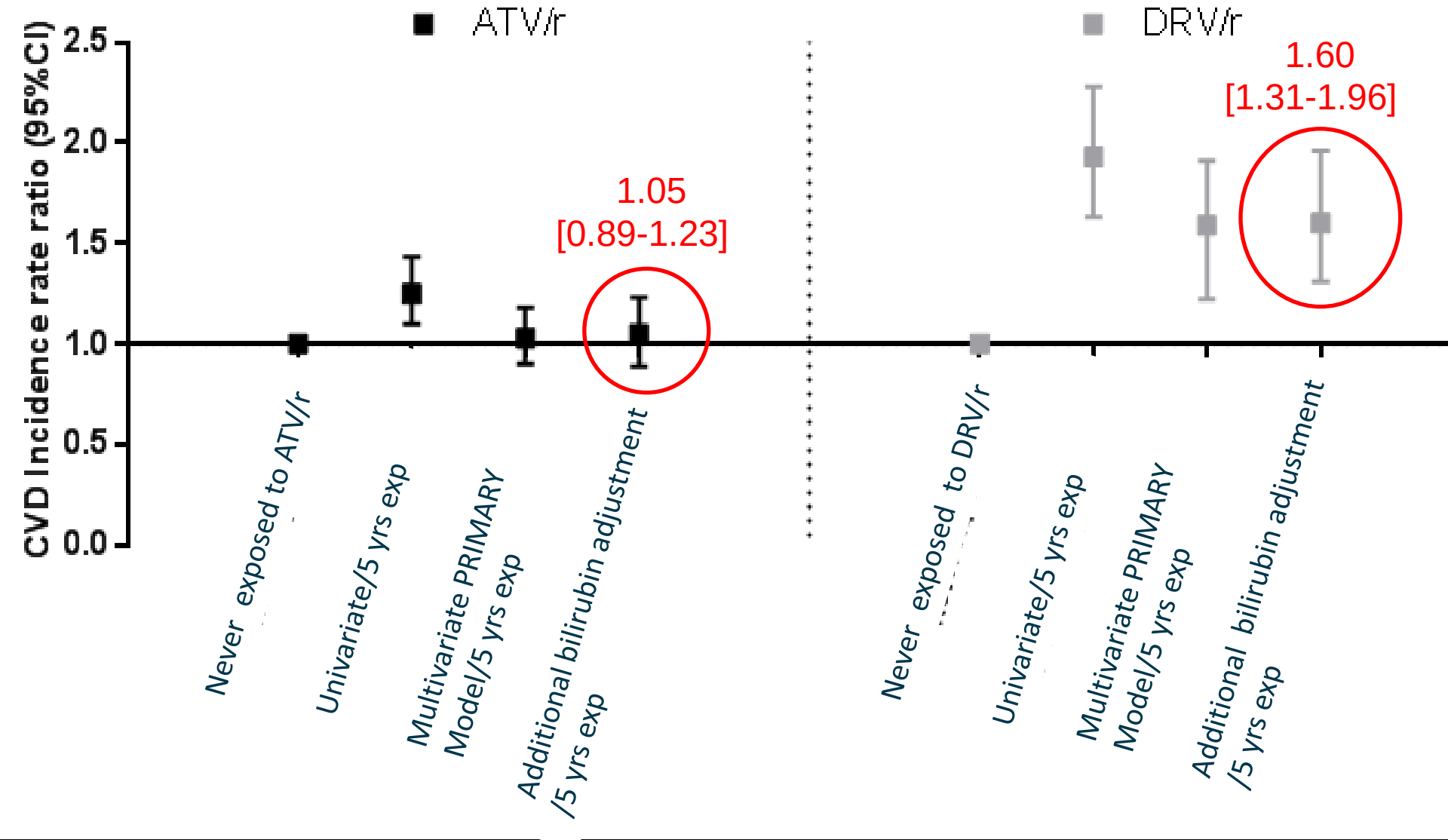
# Association Between CVD & Cumulative ATV/r and DRV/r Use;

## Additional Time-updated Adjustment for Factors Potentially on the Causal Pathway between PI/r use and CVD

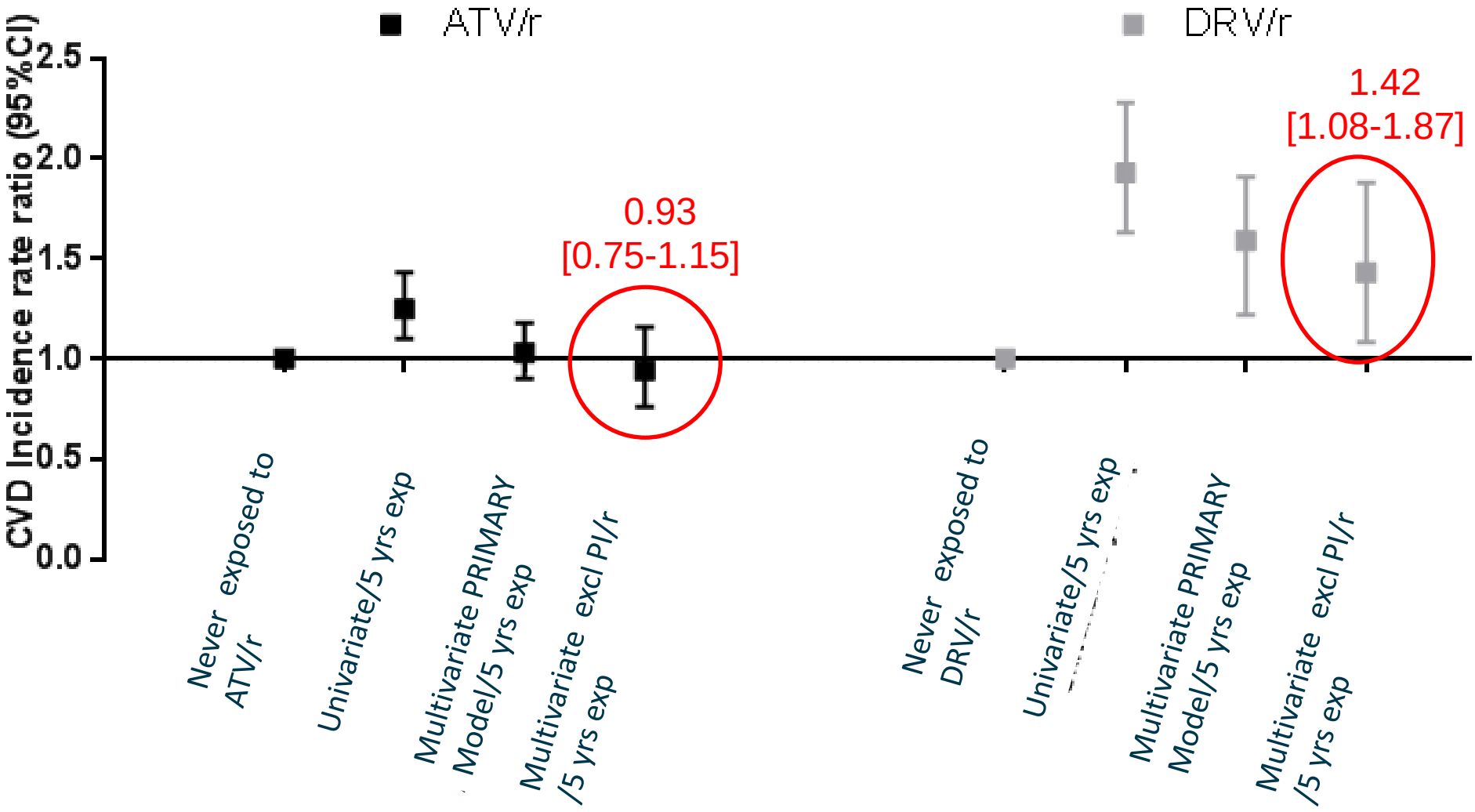
## CD4, BMI, CKD, Dyslipidaemia, Diabetes



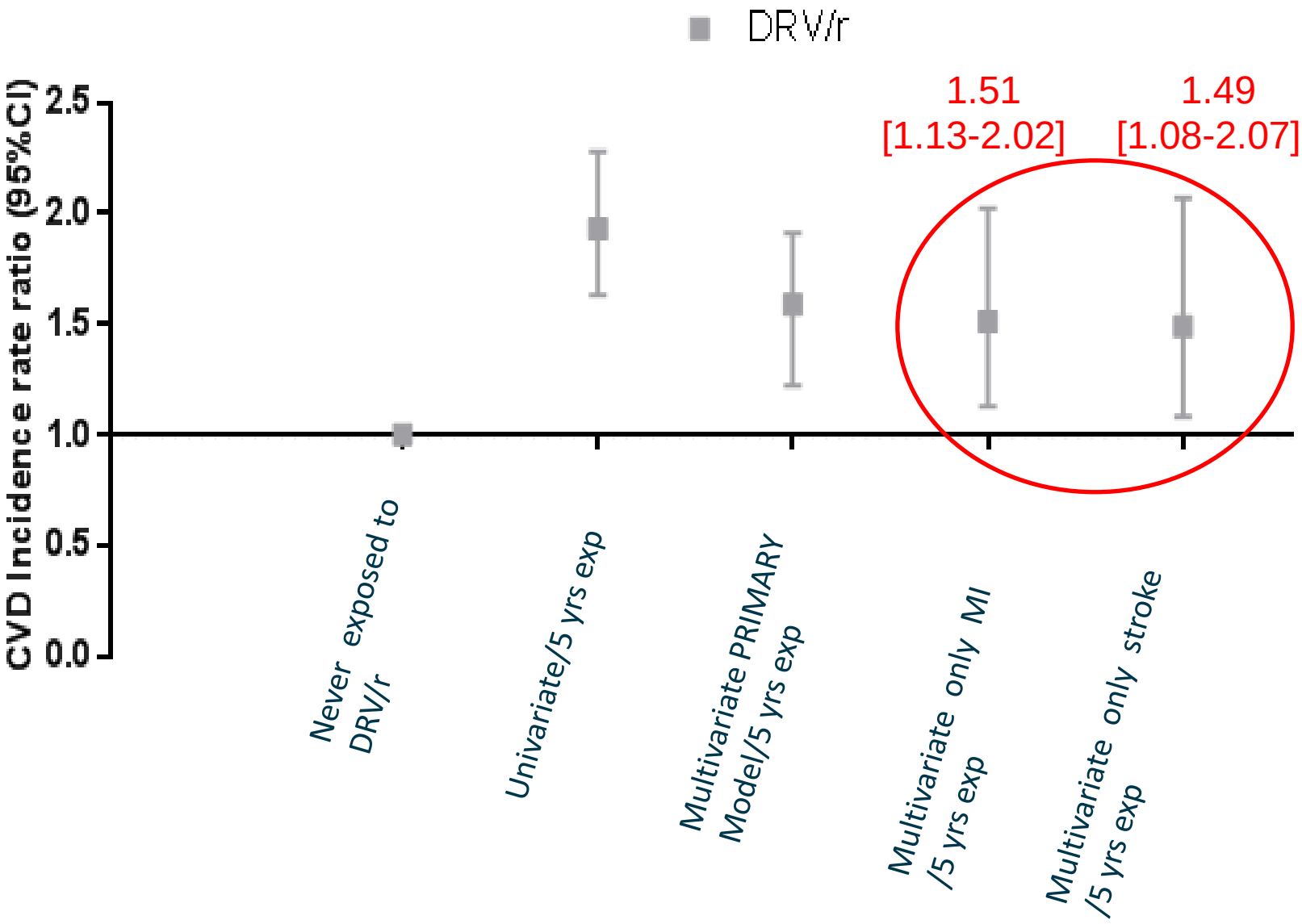
# Association Between CVD & cumulative ATV/r and DRV/r Use;
## Additional Adjustment for Bilirubin Levels (Time-updated)



# Association Between CVD & cumulative ATV/r and DRV/r Use;
## Excluding Individuals Without ATV/r and DRV/r Use



# Association Between CVD & Cumulative DRV/r Use;
## MI (n=477) and Stroke (n= 395) Separately



# Interaction Analyses

Associations were unchanged after stratification for

- Whether DRV/r was used as the first ever PI/r containing regimen or not (p=0.29 for interaction)

- Whether DRV/r was used with a non-nucleoside reverse transcriptase inhibitor or not (p=0.43 for interaction)

- Those at high vs. low estimated 5 year D:A:D CVD risk (p=0.12 for interaction)

D:A:D

# Limitations

- Inability to exclude the possibility of unmeasured confounding
- Causal inference is limited by the observational nature of our data
- No data on drug doses are collected within the D:A:D study, as such we are unable to assess if DRV/r 600/100 mg bid vs. 800/100 mg qd differ in the association with CVD
- Limited data on unboosted ATV after 2009
- Too limited follow-up data on cobicistat to enable analysis using an alternative PI boosting agent

D:A:D

# Conclusions

- In this large heterogeneous cohort of HIV-positive persons, cumulative use of DRV/r, but not ATV/r, was independently associated with a small, but gradually increasing risk of CVD of 59% per 5 years exposure

- The strength of the DRV/r association is of a similar size as found for the older PIs indinavir (IDV) and (ritonavir boosted lopinavir) LPV/r, but in contrast the DRV/r association does not seem to be modified by dyslipidemia

- Cautious interpretation is warranted due to the observational nature of the study and the risks of unmeasured confounding

- Findings call for further investigations of possible mechanisms

D:A:D

# Acknowledgements

Steering Committee: Members indicated w/ *; ¢ chair;

**Cohort PIs**: W El-Sadr* (CPCRA), G Calvo* (BASS), F Bonnet/F Dabis* (Aquitaine), O Kirk*/ A Mocroft* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (Brussels)

**Cohort coordinators & data managers**: A Lind-Thomsen (coordinator), R Salbøl Brandt, M Hillebreght, S Zaheri, FWNM Wit (ATHENA), A Scherrer, F Schöni-Affolter, M Rickenbach (SHCS), A Travelli, I Fanti (ICONA), O Leleux, E Boerg, J Mourali, F Le Marec, E Boerg (Aquitaine), E Thulin, A Sundström (HIVBIVUS), G Bartsch, G Thompsen (CPCRA), C Necsoi, M Delforge (Brussels), E Fontas, C Caissotti, K Dollet (Nice), S Mateu, F Torres (BASS), K Petoumenos A Blance, R Puhr (AHOD), K Grønborg Laut, D Kristensen (EuroSIDA)

**Statisticians**: CA Sabin*, AN Phillips*, DA Kamara, CJ Smith, A Mocroft*

**D:A:D coordinating office**: CI Hatleberg, L Ryom, A Lind-Thomsen, RS Brandt, D Raben, C Matthews, A Bojesen, AL Grevsen, JD Lundgren*¢

**Member of the D:A:D Oversight Committee**: B Powderly*, N Shortman*, C Moecklinghoff*, G Reilly*, X Franquet*

**D:A:D working group experts**:

**Kidney**: L Ryom, A Mocroft*, O Kirk*, P Reiss*, C Smit, M Ross, CA Fux, P Morlat, E Fontas, DA Kamara, CJ Smith, JD Lundgren*¢ **Mortality**: CJ Smith, L Ryom, CI Hatleberg, AN Phillips*, R Weber*, P Morlat, C Pradier*, P Reiss*, FWNM Wit, N Friis-Møller, J Kowalska, JD Lundgren*¢ **Cancer**: CA Sabin*, L Ryom, CI Hatleberg, M Law*, A d'Arminio Monforte*, F Dabis*, F Bonnet, P Reiss*, FWNM Wit, CJ Smith, DA Kamara, J Bohlius, M Bower, G Fätkenheuer, A Grulich, JD Lundgren*¢

**External endpoint reviewer**: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology)

**Funding**: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMA and a consortium of AbbVie, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck and Janssen Pharmaceuticals. Also supported by a grant [grant number DNRF126] from the Danish National Research Foundation

D:A:D