

ASSOCIATION BETWEEN INTEGRASE STRAND TRANSFER INHIBITORS AND CARDIOVASCULAR DISEASE

Bastian Neesgaard *on behalf of the RESPOND study group*

*CHIP, Dept. of Infectious Diseases Section 2100,
Rigshospitalet, Copenhagen, Denmark*

Disclosure: Nothing to disclose



Introduction:

Background:

- Associations between cardiovascular disease (CVD) and use of older antiretroviral drugs are well described,^[1] as either of:
 - Gradual increased risk with longer cumulative exposure (i.e. certain protease inhibitors). [2-4]
 - Rapid and maintained increased risk, reversible upon discontinuation (i.e. abacavir). [5-7]
- There are limited data on potential associations between longer-term exposure to integrase strand transfer inhibitors (INSTIs) and CVD.

Study objectives:

- To assess if exposure to INSTIs* (raltegravir [RAL], elvitegravir [EVG/c] and dolutegravir [DTG]), is associated with an increased incidence of CVD.

References:

1: F. Islam et al. *HIV medicine* 2012; 2: N. Friis-Moller et al. *NEJM*, 2004; 3: N. Friis-Moller et al. *NEJM*, 2007; 4: L. Ryom et al. *Lancet HIV*, 2018; 5: C. Sabin et al. *Lancet*, 2008; 6: J. Lundgren et al. *AIDS*, 2008; 7: S. Worm et al. *J Infect Dis*, 2010.

* Due to low number of individuals exposed, bictegravir was not included in the analysis



Methods:

Inclusion:

- INSTI naïve RESPOND participants [1-2] aged ≥ 18 years, followed from latest of cohort enrolment or 1st of January 2012 (baseline).

Outcomes:

- CVD - composite endpoint consisting of rigorously defined myocardial infarction (MI), strokes, and invasive cardiovascular procedures (ICP)

Statistical analysis:

- Individuals were followed from baseline to the earliest of first CVD event, last follow-up or 1st of October 2018.
- Exposure to INSTIs was calculated following the methodology developed in D:A:D study. [3]
- Negative binomial regression models, adjusted for common CVD risk factors, HIV characteristics and ARVs previously associated with CVD - factors potentially associated with INSTI use and CVD were fixed at baseline.
- Logistic regression examined odds of starting an INSTI by D:A:D 5-year CVD risk score.



Results:

- A total of **21,267** participants were included; **9,782 (46%)** exposed to an INSTI during follow-up. (**6372** to DTG, **2385** to EVG/c and **2147** to RAL)
- Overall, **75.5% were white, 73.3% male, 48.9% of Western European origin and 41.2% MSM.**
- During a **median of 6.3 years** of follow-up (IQR 3.5-6.7; 106,870 PYFU); **517 CVD events (IR 4.9/1000 PYFU [CI 95%, 4.5-5.3])** of which, **210 MIs, 162 strokes and 145 ICPs.**
- Individuals experiencing CVD were older (**median, [IQR]: 53.7 [48.5-61.9] vs. 44.5 [36.2-51.5] years**), and a larger proportion had classic risk factors for CVD at baseline, than those without.
 - Greater proportion with a high/very high **5-year estimated D:A:D CVD risk score** in the group that experienced CVD (**46% vs 12%, P<0.001**).
- **Odds ratio*** [95%CI] of initiation INSTI by 5-year estimated D:A:D CVD risk, when compared to all compared to low risk (<1%):
 - Moderate risk (1 - <5%): **1.11 [1.00-1.21]**, high risk (5 - <10%): **1.19 [1.05-1.35]**, very high risk (>10%): **1.05 [0.89-1.25]**.



Results:

Figure A:
Crude incidence rates of CVD stratified by INSTI exposure

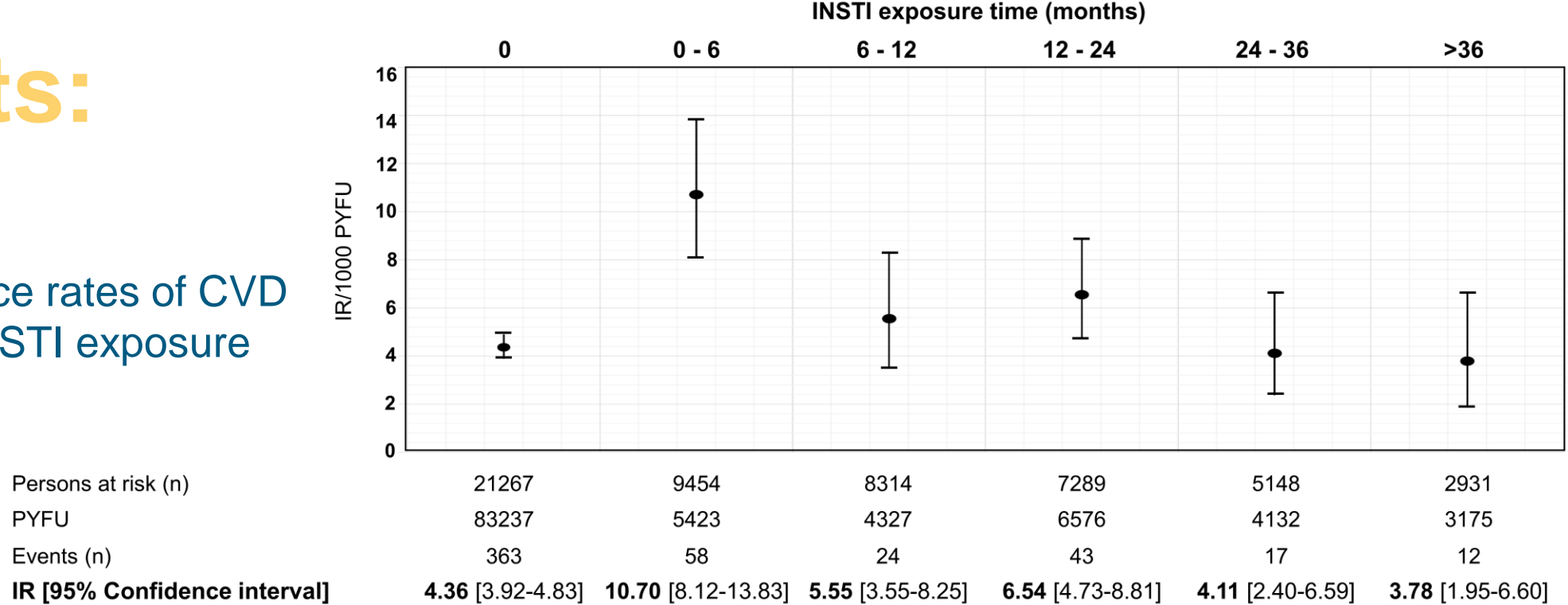
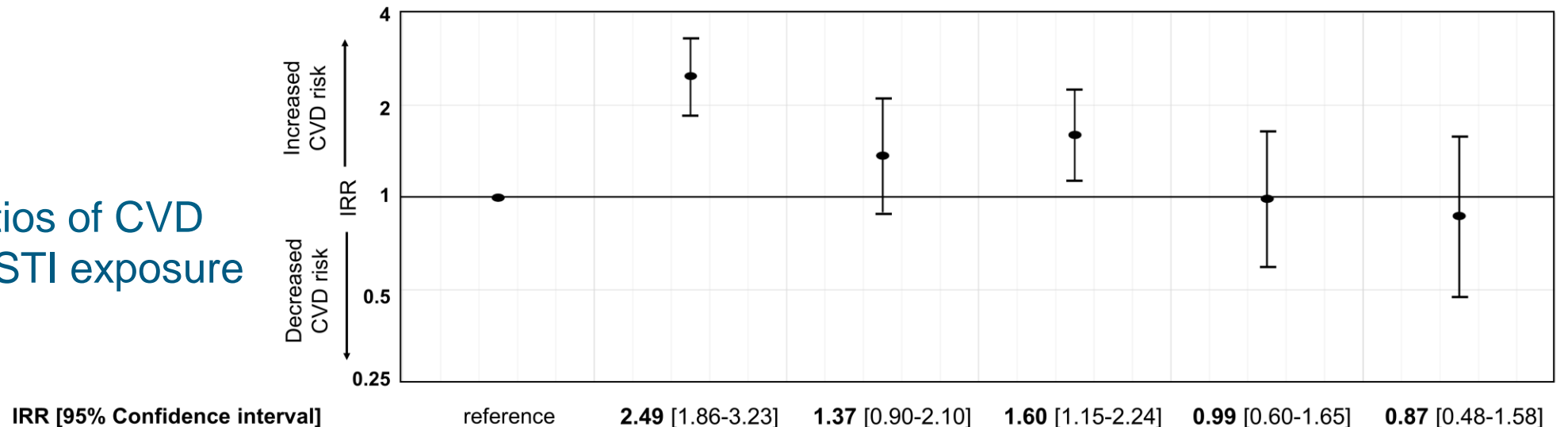


Figure B:
Adjusted IR ratios of CVD stratified by INSTI exposure



Limitations & Conclusion:

Limitations:

- Due to the observational nature of the study, we cannot exclude the potential for channeling bias or residual confounding.
- Focus on INSTI class rather than individual drugs, and unable to specifically assess ART-naïve individuals due to limited statistical power.

Conclusion:

- The INSTIs examined were associated with a 2.5 times greater incidence of CVD in the first 6 months of exposure when compared to no INSTI exposure, after accounting for known CVD risk factors, and across a wide range of sensitivity analyses.
- These findings call for further investigations in mechanistic studies and other large populations of people living with HIV seen in routine clinical care.

Writing group:

B. Neesgaard*, L. Greenberg, L. Rasmussen, H. Günthard, K. Grabmeier-Pfistershammer, S. De Wit, F Wit, A. Castagna, C. Mussini, C. Pradier, A. Sönnnerborg, A. Volny Anne, C. Smith, A. Carr, A. Pelchen-Matthews, L. Bansi-Matharu, H. Garges, F. Rogatto, J. Lundgren, L. Peters, C. Necsoi, P. Reiss, C. Muccini, M. Menozzi, J.Miro, G. Wandeler, R. Zangerle, A. Mocroft and L. Ryom.

Acknowledgements:

The RESPOND study group (<https://chip.dk/Research/Studies/RESPOND/Study-group>)

