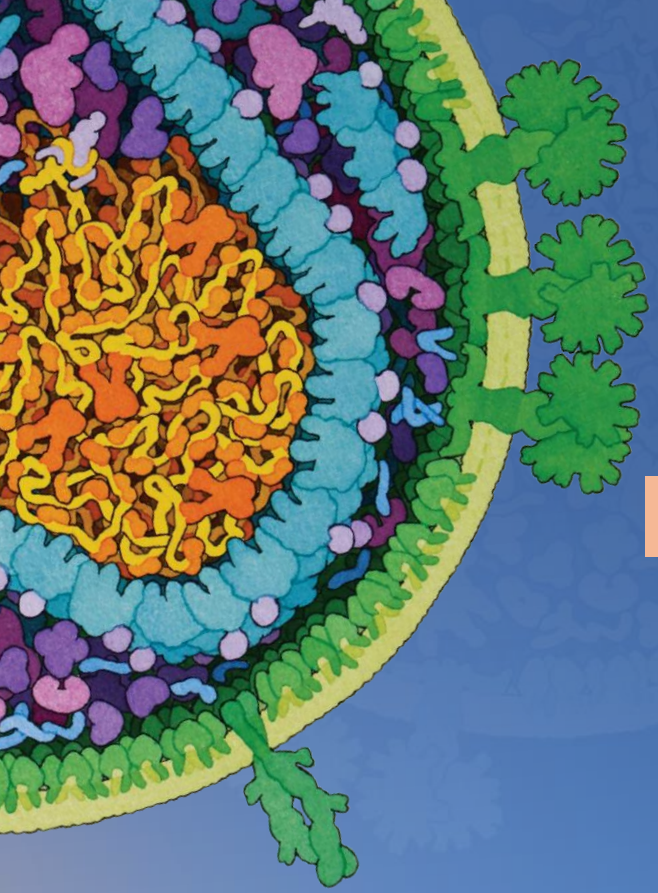

SCIENCE SPOTLIGHT™

ASSOCIATION BETWEEN INTEGRASE STRAND TRANSFER INHIBITORS AND CARDIOVASCULAR DISEASE

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Introduction:

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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:

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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.

***References**: **1**: Neesgaard et al. Microorganisms, 2020; **2:** https://chip.dk/Research/Studies/RESPOND **3**: N. Friis-Moller et al. NEJM, 2004;*

Results:

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- 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.**

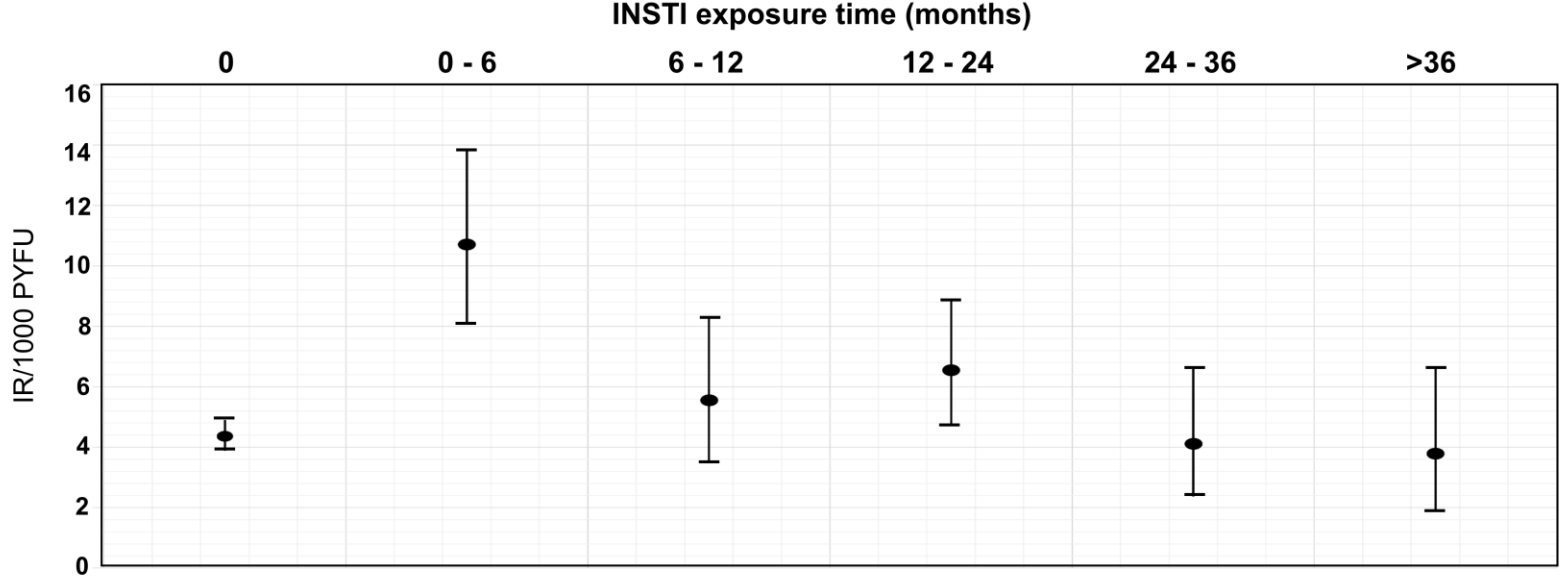
- During a **median of 6.3 years** of follow-up (IQR 3.5-6.7; 106,870 PYFU); **517** CVD events (**IR 4.9/1000 PYFU** [CI 95%, 4.5-5.3]) of which, **210 MIs, 162 strokes** and **145 ICPs.**

- 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].

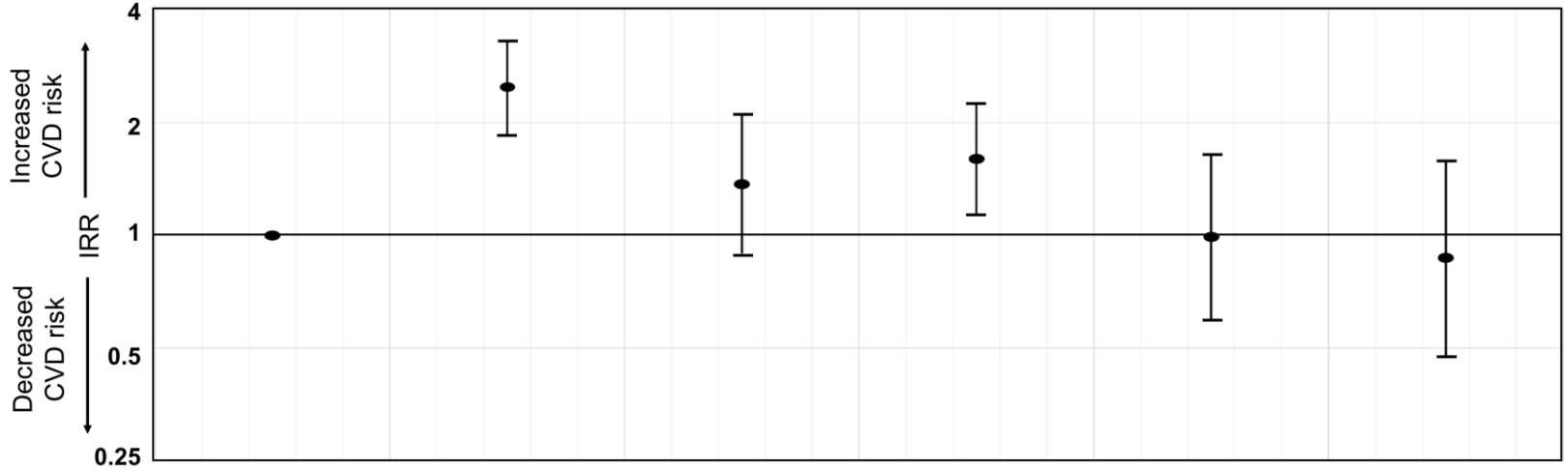
Results:

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



	0	0 - 6	6 - 12	12 - 24	24 - 36	>36
Persons at risk (n)	21267	9454	8314	7289	5148	2931
PYFU	83237	5423	4327	6576	4132	3175
Events (n)	363	58	24	43	17	12
IR [95% Confidence interval]	**4.36** [3.92-4.83]	**10.70** [8.12-13.83]	**5.55** [3.55-8.25]	**6.54** [4.73-8.81]	**4.11** [2.40-6.59]	**3.78** [1.95-6.60]

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



	0	0 - 6	6 - 12	12 - 24	24 - 36	>36
IRR [95% Confidence interval]	reference	**2.49** [1.86-3.23]	**1.37** [0.90-2.10]	**1.60** [1.15-2.24]	**0.99** [0.60-1.65]	**0.87** [0.48-1.58]

Multivariable model adjusted for: Baseline: Calendar year, age, gender, ethnicity, region, body mass index, HIV acquisition risk, antiretroviral treatment status, CD4 count, hypertension, diabetes, prior AIDS, cardiovascular disease, chronic kidney disease and dyslipidaemia. Time-updated: Smoking status, cumulative exposure to lopinavir, indinavir, didanosine, stavudine, darunavir and abacavir use in the past 6 months

Limitations & Conclusion:

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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:
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