Evaluating the impact of integrase inhibitors on cardiovascular disease events: A causal inference analysis in RESPOND

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BACKGROUND

- People with HIV have an increased risk of cardiovascular disease (CVD) compared to the general population.[1]
- The RESPOND cohort[2] found that use of integrase inhibitors (INSTIs) may increase relative CVD risk vs. other antiretroviral therapy (ART).[3] Other studies applying different methodologies have yielded mixed results.[4-8]
- We re-analysed the original RESPOND data, comparing individuals initiating or switching to INSTI-based ART versus other ART regimens using a target trial framework to assess how methodological choices influence these findings.

METHODS

- Using RESPOND data, a large European and Australian cohort collaboration between 19 cohorts, including > 45.000 people with HIV seen in routine clinical care, we emulated two target trials :
  - (1) treatment-naïve individuals initiating ART, and (2) ART-experienced individuals with a suppressed HIV viral load

Treatment-Naïve Analysis

- Inclusion: ART-naïve after January 2012 with detectable HIV viraemia. Baseline: start date of the initial ART regimen

Treatment-Experienced Analysis

- Inclusion: on INSTI-free ART after January 2012, no prior INSTI exposure, suppressed HIV viral load, no history of CVD. Baseline: A new nested trial was emulated each month between Jan 2012 and Dec 2021; baseline was redefined, and eligibility reassessed at each trial start

Outcome:

- First CVD event (myocardial infarction, stroke, and invasive cardiovascular procedure)

Statistical Analysis

- Adjusting for potential confounding at baseline using inverse probability of treatment weighting
- For intention-to-treat analysis, we used pooled logistic regression to estimate risk differences and ratios for CVD
- In per-protocol analysis, participants were censored when they deviated from their assigned strategy. We accounted for censoring using time-updated censoring weights.

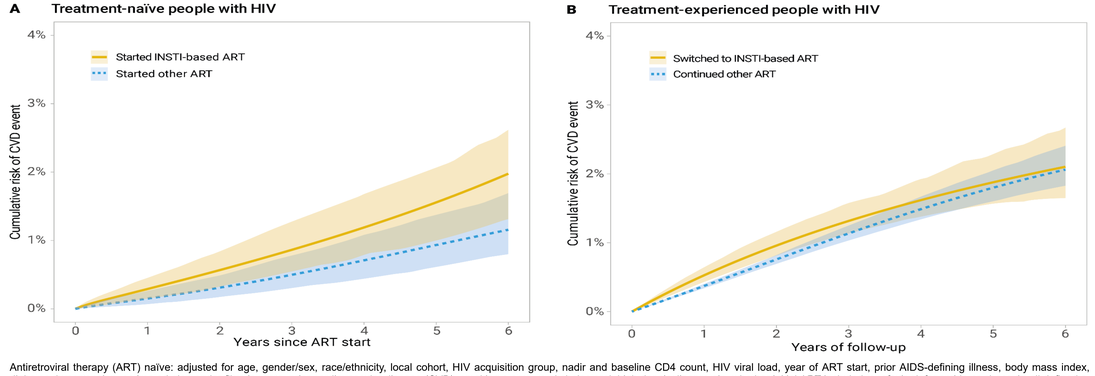
Using a target trial framework, we observed an increased relative CVD risk associated with INSTI use, among treatment-experienced individuals that decreased over time, consistent with prior analyses.

However, the absolute risk increase was small and given the substantial benefits of INSTI-based ART, INSTIs should remain recommended until this signal is consistently confirmed in other cohorts.

Future pharmacovigilance should focus on individual INSTIs, targeted subgroup analyses, and mechanistic studies to clarify potential causal pathways.

RESULTS

- In both ART-naïve and ART-experienced analyses, the CVD risk at baseline was higher among those starting/switching to INSTIs.
- Among 7111 ART-naïve participants (19% women, median age 38 years, 27% with a CD4 count <200 cells/μL), 3354 (47%) started INSTIs (dolutegravir [DTG, 55%], elvitegravir [EVG/c 19%], raltegravir [RAL, 17%], bictegravir [BIC 8.5%]) and 3757 non-INSTIs (most common: darunavir [DRV/b, 30% efavirenz [EFV, 25%], rilpivirine [RPV, 22%], atazanavir [ATV/b, 9%]). During a median follow-up of 62 months, 95 CVD events occurred. Adjusted RRs comparing those starting INSTI vs other ART were 1.92 (95% CI 0.82–4.31) at 1 year, 1.83 (0.83–3.68) at 2 years, and 1.71 (0.99–3.04) at 6 years (Table).
- Among ART-experienced, 22921 persons (28% women, median age 49 years, 70 % with a CD count >500 cell/μL), 11278 of whom switched to INSTIs (DTG 58%, EVG 18.1%, RAL16.1%, BIC 7.6%) and 11643 to a non-INSTIs (most common: EFV 23%, DRV/b 17%, RPV 14%, nevirapine 14%, ATV/b 10%, and lopinavir 5%), were followed for a median 37 months (IQR 18–63). In total, 800 CVD events occurred; adjusted RRs were 1.41 (95% CI, 1.20–1.74), 1.26 (1.07–1.52), and 1.02 (0.80–1.28) at 1, 2, and 6 years, respectively. (Table).
- The absolute risk difference remained small throughout, not exceeding 1.23 percentage points, for both treatment-naïve (Figure A) and treatment-experienced individuals (Figure B).



Antiretroviral therapy (ART) naïve: adjusted for age, gender/sex, race/ethnicity, local cohort, HIV acquisition group, nadir and baseline CD4 count, HIV viral load, year of ART start, prior AIDS-defining illness, body mass index, diabetes, hypertension, estimated glomerular filtration rate, prior cardiovascular disease (CVD), smoking status, total cholesterol, high density lipoprotein, whether initial ART included tenofovir alafenamide or abacavir; all defined at base-line. ART-experienced: Adjusted for the same covariates, except prior CVD and baseline HIV viral load were removed, and year of ART start and an indicator for each nested trial.

Treatment–naïve individuals

Analysis	Time (years)	Risk for CVD events: Started INSTI (95% CI)	Started other ART (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Intention to treat	1	0.29% (0.15 – 0.45)	0.15% (0.07 – 0.26)	0.14% (-0.04 – 0.32)	1.92 (0.82 – 4.31)
	2	0.57% (0.33 – 0.84)	0.31% (0.17 – 0.49)	0.26% (-0.07 – 0.56)	1.83 (0.83 – 3.68)
	4	1.19% (0.79 – 1.68)	0.71% (0.44 – 1.08)	0.48% (-0.08 – 1.00)	1.68 (0.92 – 3.22)
	6	1.98% (1.31 – 2.62)	1.16% (0.80 – 1.69)	0.82% (-0.02 – 1.66)	1.71 (0.99 – 3.04)
Per protocol	1	0.24% (0.08 – 0.39)	0.09% (0.01 – 0.34)	0.15% (-0.15 – 0.33)	2.60 (0.38 – 20.81)
	2	0.51% (0.25 – 0.74)	0.21% (0.05 – 0.79)	0.30% (-0.37 – 0.57)	2.44 (0.53 – 11.72)
	4	1.19% (0.75 – 1.56)	0.52% (0.18 – 1.42)	0.67% (-0.46 – 1.18)	2.28 (0.66 – 6.04)
	6	2.15% (1.27 – 3.17)	0.92% (0.41 – 2.25)	1.23% (-0.23 – 2.31)	2.34 (0.86 – 4.83)

Treatment–experienced with HIV

Analysis	Time (years)	Risk for CVD events: Switch to INSTI (95% CI)	Remained on Other ART (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Intention to treat	1	0.53% (0.42 – 0.64)	0.37% (0.34 – 0.40)	0.15% (0.07 – 0.27)	1.41 (1.19 – 1.71)
	2	0.96% (0.80 – 1.14)	0.76% (0.69 – 0.82)	0.20% (0.05 – 0.38)	1.26 (1.07 – 1.52)
	4	1.62% (1.37 – 1.91)	1.49% (1.33 – 1.67)	0.13% (-0.10 – 0.41)	1.09 (0.93 – 1.29)
	6	2.10% (1.63 – 2.64)	2.06% (1.82 – 2.40)	0.04% (-0.44 – 0.59)	1.02 (0.79 – 1.28)
Per protocol	1	0.78% (0.64 – 0.94)	0.45% (0.41 – 0.49)	0.33% (0.17 – 0.48)	1.74 (1.37 – 2.09)
	2	1.36% (1.14 – 1.57)	0.90% (0.82 – 1.00)	0.45% (0.22 – 0.67)	1.50 (1.21 – 1.80)
	4	2.25% (1.92 – 2.54)	1.84% (1.65 – 2.09)	0.41% (0.03 – 0.80)	1.22 (1.02 – 1.49)
	6	3.14% (2.74 – 3.52)	2.83% (2.43 – 3.31)	0.32% (-0.29 – 0.91)	1.11 (0.91 – 1.35)

INSTI = integrase strand transfer inhibitor, **ART** = antiretroviral therapy, **CI** = confidence interval. **CVD**= Cardiovascular disease

LIMITATIONS

- Potential for confounding by indication, and residual confounding by unmeasured factors.
- We can not exclude that potential selection bias may have influenced our results

CONCLUSIONS

- Consistent with our initial results, INSTI exposure in ART-experienced individuals was associated with an increased relative risk of CVD in the first two years compared with other ART.
- Among ART-naïve individuals, a trend toward increased risk was observed, although not statistically significant, likely due to lower power.
- Further research is needed to evaluate individual INSTIs and investigate potential underlying causal biological mechanisms.

RESPOND Study Group: https://chip.dk/Research/Studies/RESPOND/Study-group

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