Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium

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Summary

Background Although associations between older antiretroviral drug classes and cardiovascular disease in people living with HIV are well described, there is a paucity of data regarding a possible association with integrase strand-transfer inhibitors (INSTIs). We investigated whether exposure to INSTIs was associated with an increased incidence of cardiovascular disease.

Methods RESPOND is a prospective, multicentre, collaboration study between 17 pre-existing European and Australian cohorts and includes more than 32 000 adults living with HIV in clinical care after Jan 1, 2012. Individuals were eligible for inclusion in these analyses if they were older than 18 years, had CD4 cell counts and HIV viral load measurements in the 12 months before or within 3 months after baseline (latest of cohort enrolment or Jan 1, 2012), and had no exposure to INSTIs before baseline. These individuals were subsequently followed up to the earliest of the first cardiovascular disease event (ie, myocardial infarction, stroke, or invasive cardiovascular procedure), last follow-up, or Dec 31, 2019. We used multivariable negative binomial regression to assess associations between cardiovascular disease and INSTI exposure (0 months [no exposure] *vs* >0 to 6 months, >6 to 12 months, >12 to 24 months, >24 to 36 months, and >36 months), adjusted for cardiovascular risk factors. RESPOND is registered with ClinicalTrials.gov, NCT04090151, and is ongoing.

Findings 29 340 people living with HIV were included in these analyses, of whom 7478 (25·5%) were female, 21 818 (74·4%) were male, and 44 (<1%) were transgender, with a median age of 44·3 years (IQR 36·2–51·3) at baseline. As of Dec 31, 2019, 14 000 (47·7%) of 29 340 participants had been exposed to an INSTI. During a median follow-up of 6·16 years (IQR 3·87–7·52; 160 252 person-years), 748 (2·5%) individuals had a cardiovascular disease event (incidence rate of 4·67 events [95% CI 4·34–5·01] per 1000 person-years of follow-up). The crude cardiovascular disease incidence rate was 4·19 events (3·83–4·57) per 1000 person-years in those with no INSTI exposure, which increased to 8·46 events (6·58–10·71) per 1000 person-years in those with more than 0 months to 6 months of exposure, and gradually decreased with increasing length of exposure, until it decreased to similar levels of no exposure at more than 24 months of exposure (4·25 events [2·89–6·04] per 1000 person-years among those with >24 to 36 months of exposure). Compared with those with no INSTI exposure, the risk of cardiovascular disease was increased in the first 24 months of INSTI exposure and thereafter decreased to levels similar to those never exposed (>0 to 6 months of exposure: adjusted incidence rate ratio of 1·85 [1·44–2·39]; >6 to 12 months of exposure: 1·19 [0·84–1·68]; >12 to 24 months of exposure: 1·46 [1·13–1·88]; >24 to 36 months of exposure: 0·89 [0·62–1·29]; and >36 months of exposure: 0·96 [0·69–1·33]; p<0·0001).

Interpretation Although the potential for unmeasured confounding and channelling bias cannot fully be excluded, INSTIs initiation was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors. These early findings call for analyses in other large studies, and the potential underlying mechanisms explored further.

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Research in context

Evidence before this study

We searched PubMed for observational studies and clinical trials published since database inception to Aug 1, 2021, without any language restrictions, using the MeSH terms "cardiovascular disease", OR "myocardial infarction" OR "cerebrovascular disorder" OR "stroke" OR "cardiovascular procedures" AND "antiretroviral therapy, highly active" OR "anti-retroviral agents" OR "HIV integrase inhibitors" OR "raltegravir" OR "elvitegravir" OR "dolutegravir" OR "bictegravir," AND "HIV". Associations between the risk of cardiovascular disease and the use of older antiretroviral drugs are well described. The risk has been described as a gradual increase with longer cumulative exposures for the boosted protease inhibitors indinavir, lopinavir, and darunavir, and as a rapid and maintained risk increase, reversible upon discontinuation, for the nucleotide reverse-transcriptase inhibitor abacavir. However, investigations of a potential association between the use of the newer integrase inhibitor drug class (which are recommended as first-line treatment in most guidelines) and cardiovascular disease are still scarce. Well powered studies with rigorously defined endpoints are needed to determine whether an association exists between cumulative exposure to integrase inhibitors and cardiovascular disease.

Added value of this study

To our knowledge, this is the first assessment of cardiovascular disease events and exposure to integrase strand-transfer inhibitors from a large heterogeneous cohort of people living with HIV with prospective data collection. When comparing individuals never exposed to an integrase inhibitor to individuals exposed for more than 0 months to 6 months, more than 6 months to 12 months, more than 12 months to 24 months, more than 24 months to 36 months, and for more than 36 months, we found that the adjusted incidence rate ratio of cardiovascular disease was 1·85 in the first 6 months of exposure, after adjustment for potential confounders. The association remained until 24 months of exposure, although at a lower relative risk than in the initial 6 months.

Implications of all the available evidence

With cardiovascular disease remaining a common cause of morbidity and mortality among people living with HIV, treatment given to suppress HIV must not add to the cardiovascular risk profile. Therefore, insights into cardiovascular disease risk factors, including the potential role of individual antiretroviral agents, remain crucial. Our results call for investigations in other large studies and further exploration of potential mechanisms underlying the increased relative cardiovascular risk we found here.

Introduction

With combination antiretroviral therapy (ART), life expectancy among people living with HIV has approached that of the HIV-negative population.[1] Yet, as the global population ages, non-AIDS comorbidities such as cardiovascular disease and related risk factors are being seen with increasing frequency.[2] Therefore, continuous assessments of modern antiretroviral drugs are needed to tailor ART regimens to fit individual needs, taking into consideration the complex interactions between ART, comorbidities, lifestyle factors, and non-ART medication.[3,4]

A safety signal linking ART exposure to incident myocardial infarction was first noted in a 2003 publication from The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.[5] Follow-up studies from the same group published in 2007 and 2010 in part attributed the increase in the relative risk of myocardial infarction to the older protease inhibitors indinavir (an increase of 47% per 5 years of exposure) and ritonavir-boosted lopinavir (an increase of 54% per 5 years of exposure).[6,7] An additional analysis from the D:A:D study further suggested that current exposure or exposure within the past 6 months to the nucleoside-reverse transcriptase inhibitor, abacavir, increased the relative risk of myocardial infarction by 90%.[8] Subsequently, these findings were reproduced in other independent studies,[9] although not consistently across all studies.[10] Although a proatherosclerotic lipid profile is now generally considered to underlie the association between cardiovascular disease events and older protease inhibitors,[11] a platelet hyperactivity mechanism has been suggested as the link between abacavir and cardiovascular disease.[12] Both cases illustrate that the process from initially observing a potential safety signal to establishing a plausible causal mechanism evolves over time and requires the involvement of many different types of studies. A separate report of a 59% increase in cardiovascular disease risk per 5 years of exposure to ritonavir-boosted darunavir,[13] not explained by dyslipidaemia, serves as an example of the initiation of one such process; underlining the continued need for large-scale pharmacovigilance research of potential adverse effects of antiretroviral drugs. Despite investigations, to date no studies have reported an association between cardiovascular disease and the use of non-nucleotide reverse transcriptase inhibitors.[7,13]

Due to their potent suppression of HIV viraemia, rapid immune reconstitution, and high genetic barrier to resistance,[14–17] unboosted integrase strand-transfer inhibitors (INSTIs) are recommended as first-line treatment in North American and European guidelines.[3,4] Although INSTIs are generally well tolerated,[14–17] recent studies have suggested a possible association between INSTI use, weight gain, and metabolic syndrome[18–20]—factors that in turn could lead to cardiovascular disease. However, there is a paucity of data on the potential association between rarely occurring cardiovascular disease events and exposure to INSTIs.[21,22] Therefore,

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data from large-scale, prospective, observational collaborations with extended follow-up and rigorously defined clinical endpoints are warranted.

We investigated whether exposure to INSTIs is associated with an increased incidence of cardiovascular disease within the International Cohort Consortium of Infectious Disease (RESPOND) cohort consortium.

Methods

Study design and participants

A detailed description of RESPOND, including methods, has been published elsewhere.[23] Briefly, RESPOND was formed in 2017, dedicated to the study of HIV and other infectious diseases, as a prospectively multicentre collaboration between 17 pre-existing European and Australian cohorts. To be eligible for inclusion in RESPOND, participants need to have a clinical diagnosis of HIV, be older than 18 years, have had no exposure to INSTIs before Jan 1, 2012, and to have CD4 cell count and HIV viral load measurements in the 12 months before or within 3 months after baseline (defined as latest of cohort enrolment or Jan 1, 2021).

Participants consented to share data with RESPOND according to local requirements. Enrolled participants were pseudonymised by assigning a unique identifier by the participating cohort before data transfer to the main RESPOND database. According to national or local requirements, all cohorts had the approval to share data with RESPOND. Ethical approval was obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating centre in Copenhagen, Denmark, in accordance with current legislation and under approval by the Danish Data Protection Agency (approval number 2012-58-0004, RH-2018-15, 26/1/2018), under the EU General Data Protection Regulation (2016/679).

Procedures

Data were collected retrospectively for all included participants for at least the 5 years before their enrolment into RESPOND, with a complete history of ART and clinical events collected for all individuals. Additionally, prospective data have been collected annually since the formation of RESPOND. Data were systematically collected on demographics (eg, sex, age, and geographical region of origin), viral hepatitis coinfection status, and HIV-specific information (eg, HIV viral load, CD4 cell counts, and AIDS diagnoses), and detailed information on ART including start and stop dates and reasons for discontinuation. Furthermore, data were collected on non-ART medication, biochemical measures (eg, lipids, creatinine, glucose, and glycated haemoglobin), cardiovascular risk factors (previous cardiovascular disease, smoking, body-mass index [BMI], hypertension, renal function, and diabetes), and incident clinical events (including cardiovascular disease, cancers, and liver and renal failure).

Outcomes

We assessed cardiovascular disease using a composite endpoint consisting of fatal and non-fatal myocardial infarctions, strokes, and invasive cardiovascular procedures (ie, coronary angioplasty or stenting, coronary bypass surgery, and carotid endarterectomy). Cardiovascular disease events occurring within 12 months of the last clinical visit before RESPOND enrolment and thereafter were reported using designated case report forms. Subsequently, the case report forms were centrally validated by a trained medical doctor using standardised algorithms based on WHO's MONICA study.[24] Cardiovascular disease events occurring before this timepoint were collected but not centrally validated. This standardised algorithm ensures that only ischaemic cardiovascular disease events and cerebral haemorrhages are accepted as cardiovascular disease events within RESPOND (eg, non-ischaemic type II myocardial infarction, diagnostic angiography, or transient cerebral ischaemia are not considered cardiovascular disease events).

Statistical analysis

We used descriptive statistics to describe baseline demographic and clinical characteristics. Between patients with and without a cardiovascular disease events, we did comparisons of baseline categorical variables using the χ^2 test and for continuous variables using the Wilcoxon-Mann-Whitney non-parametric test.

We followed up individuals naive to INSTIs in the RESPOND study from baseline (ie, latest of cohort enrolment or Jan 1, 2012), to the earliest of the first cardiovascular disease event (ie, myocardial infarction, stroke, or invasive cardiovascular procedure), last follow-up visit, or Dec 31, 2019 (administrative censoring date). We allowed inclusion of individuals with a cardiovascular event before baseline, but only included incident events of a different subtype after baseline (eg, if a participant had a myocardial infarction before baseline, we would not include a subsequent myocardial infarction during follow-up, whereas we would count a stroke). We did not count invasive cardiovascular procedures done within 72 h of a myocardial infarction or stroke.

We used logistic regression, adjusted for calendar time, to assess whether or not individuals at a higher estimated 5-year D:A:D cardiovascular disease risk (where a <1% D:A:D 5-year risk score is low risk, 1% to <5% is moderate risk, 5% to <10% is high risk, and ≥10% is very high risk)[25] preferentially started an INSTI compared with other contemporary third-drug antiretrovirals within the period. We did this analysis for both the overall cohort and restricted to only include those who were ART experienced. We used the 5-year risk estimate, rather than the 10-year risk estimate, because the median follow-up duration in the population did not exceed 10 years.

We calculated ART exposure on the basis of the D:A:D study methods, described elsewhere.[5] Briefly,

follow-up from each participant was divided into a series of consecutive 1 month periods, adding each month on a drug, the person's cumulative exposure for that specific drug. If treatment stopped, the exposure count remained static with no addition to the cumulative exposure of that drug. However, should the specific treatment be reinitiated, time would be added to the cumulative exposure. We repeated this process for each antiretroviral drug that an individual had received. Finally, we added drug exposure before baseline to the cumulative exposure.

In these first assessments of a potential association between INSTI exposure and cardiovascular disease events within RESPOND, we assessed INSTI exposure as a class exposure consisting of raltegravir, cobicistat-boosted elvitegravir, dolutegravir, and bictegravir, because the analytical power at the time of the analysis was insufficient to assess exposure to individual INSTIs. In post-hoc power calculation, we found less than 50% power to detect a 1·8-times increase in the incidence of cardiovascular disease in the first 6 months of exposure to the most frequently used INSTI in RESPOND, dolutegravir, versus those not exposed to dolutegravir. On the basis of exploratory analyses to determine whether a potential association between incidence of cardiovascular disease and exposure to INSTI was linear or not (not presented here), we analysed INSTI exposure as a categorical variable, with categories of 0 months (unexposed), more than 0 months to 6 months, more than 6 months to 12 months, more than 12 months to 24 months, more than 24 months to 36 months, and more than 36 months of exposure. The 0 month exposure group refers to participants who were never exposed to an INSTI, at any time, and per definition, includes both ART-naive and ART-exposed individuals. Because the RESPOND dataset has complete ART history and precise dates of cardiovascular disease events, we were able to determine INSTI duration of exposure before cardiovascular disease events for those exposed to INSTIs.

We calculated cardiovascular disease incidence rates per 1000 person-years of follow-up, stratified by duration of exposure to INSTIs.

We used binomial regression models using generalised estimating equations and robust standard errors to examine a potential association between incidence of cardiovascular events and exposure to INSTIs. We adjusted the model for the following prespecified factors: sex (male and female), race (Black, White, and other), region (west Europe, south Europe and Argentina, north Europe and Australia, and east Europe), HIV acquisition risk (men who have sex with men, heterosexual contact, and intravenous drug use), age (per 10 years older), BMI (<18·5, 18·5 to <25, 25 to <30, and >30 kg/m²), CD4 count (per 100 cells per µL higher), CD4 nadir (per 100 cells per µL higher), hypertension (yes and no), dyslipidaemia (yes and no), diabetes (yes and no), previous AIDS-defining conditions (yes and no), previous cardiovascular disease (before baseline; yes and no), and chronic kidney disease (yes and no), all fitted at baseline. We included smoking (never, current, and previous) and antiretroviral drugs previously associated with cardiovascular disease (cumulative exposure to indinavir, ritonavir-boosted lopinavir, boosted darunavir, didanosine, and recent abacavir exposure [current or within 6 months]) in the model as time-updated variables. For missing categorical data, we included an unknown category in the model. Due to collinearity with cumulative ART exposure, we did not include calendar year or treatment experience in the model.

To investigate the potential overfitting of the model, we did a sensitivity analysis in which we adjusted only for the estimated 5-year D:A:D cardiovascular disease risk score.[25] We did exploratory analyses to assess the effect of fitting factors on the potential causal pathway from INSTI exposure to cardiovascular disease (CD4 cell count, BMI, hypertension, diabetes, chronic kidney disease, and dyslipidaemia) as time-updated variables to assess if this would attenuate a potential signal and indicate a mediator effect. Subsequently, we added time-updated platelet counts to the model, assessing a potential platelet-dependent mechanism, such as blood clotting.

To test the primary model's robustness, we also did sensitivity analyses with a model that excluded invasive cardiovascular procedures from the composite cardiovascular disease endpoint and a model that excluded individuals with any cardiovascular disease events before baseline. We also did sensitivity analyses including only included centrally validated cardiovascular disease events and individuals who switched or initiated a new ART regimen after Jan 1, 2012.

We also assessed the crude incidence rate of each composite of the composite cardiovascular disease endpoint to determine whether these were equally distributed over time.

In preplanned interaction analyses, we examined if the incidence of cardiovascular disease events and association with exposure to INSTIs varied depending on the estimated 5-year cardiovascular disease risk score, sex, or age (<50 years and ≥50 years) by testing the relevant interactions. Additionally, we examined potential variation due to differences in the availability of first-generation and second-generation INSTIs by testing a potential interaction with calendar year before or after Jan 1, 2014.

We did not have adequate statistical power to stratify individuals on the basis of treatment experience at baseline; however, because of the unexpected result of the main analyses in post-hoc analysis, we tested the interaction between INSTI exposure and ART treatment experience at baseline, with groups defined as ART naive, ART experienced with a viral load of 200 copies per mL or higher, or ART experienced with a viral load of less than 200 copies per mL.

To further investigate the effect of immunological and virological status on incidence rate ratio of cardiovascular disease we did an exploratory post-hoc analysis focused

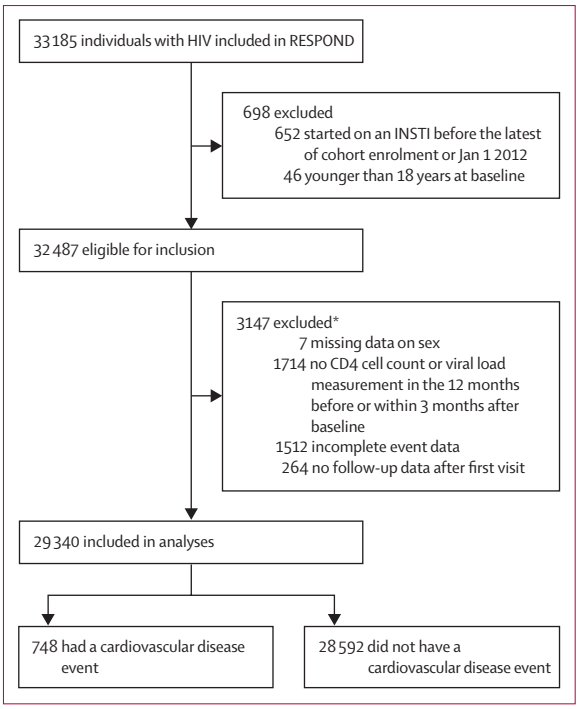

Figure 1: **Study profile**
INSTI=integrase strand-transfer inhibitor. *Individuals could have had more than one reason for exclusion.

on the first 6 months after starting an INSTI. We also stratified individuals according to good (CD4 count of ≥500 cells per μL and viral load <200 copies per mL), poor (CD4 count of ≤350 cells per μL and viral load of >200 copies per mL), or intermediate (all other combinations) immunological and virological markers[26] at the time of INSTI initiation.

We used Stata SE (version 15.0) for all analyses. All p values are two-sided, with a p value of less than 0·05 defined as significant, with global p values calculated using the Wald test. RESPOND is registered with ClinicalTrials.gov, NCT04090151.

Role of the funding source

For **RESPOND governance and procedures** see https://chip.dk/Portals/0/files/RESPOND/Study%20documents/RESPOND%20governance%20and%20procedures_v6_2020SEP30.pdf?ver=2020-10-20-163958-080

As per RESPOND governance, funders of the study were also academic collaborators, and employees or associates could be included as co-authors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof), were not in a position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Among 32 487 eligible individuals within RESPOND, 3147 participants were excluded due to missing data or measurements, leaving 29 340 (90·3%) HIV-positive individuals naive to INSTIs who were eligible for inclusion in these analyses (figure 1). A larger proportion of RESPOND participants who were excluded than were included in these analyses were naive to ART (1678 [53·3%] of 3147 *vs* 7172 [24·4%] of 29 340), and a lower proportion had one or more comorbidities (1343 [42·7%] *vs* 20 913 [71·3%]).

Among the 29 340 eligible individuals, the median age at baseline was 44·3 years (36·2–51·3), 7478 (25·5%) were female, 21 818 (74·4%) were male, 20 419 (69·6%) were White, and 2983 (10·2%) were Black (table 1). 14 000 (47·7%) individuals were exposed to one or more INSTIs during follow-up: 8647 (61·8%) of 14 000 individuals were exposed to dolutegravir, 3344 (23·9%) to cobicistat-boosted elvitegravir, 3296 (23·5%) to raltegravir, and 840 (66·0%) to bictegravir.

During a median follow-up of 6·16 years (IQR 3·87–7·52; 160 252 person-years of follow-up), 748 (2·5%) individuals had a cardiovascular disease event, of which 299 (40%) were myocardial infarctions, 228 (30%) were strokes, and 221 (30%) were invasive cardiovascular procedures, giving a crude incidence rate of 4·67 events (95% CI 4·34–5·01) per 1000 person-years of follow-up. Traditional cardiovascular disease risk factors, such as current smoking, hypertension, dyslipidaemia, chronic kidney disease, and diabetes, were more prevalent at baseline among those who had a cardiovascular disease event during follow-up (p<0·001 for all; table 1). Furthermore, individuals who had a cardiovascular disease event were generally older than those who did not have an event, and their 5-year estimated risk of cardiovascular disease at baseline was consequently higher (p<0·001). Additional details on previous ART use among those with and without incident cardiovascular disease and those exposed and unexposed to INSTIs are in the appendix (p 3).

Compared with those at low estimated 5-year risk of cardiovascular disease, the likelihood of starting an INSTI increased linearly with increasing risk of cardiovascular disease (p<0·001 for all; figure 2). The results were consistent but slightly more pronounced when only assessing ART-experienced individuals (figure 2).

The crude cardiovascular disease incidence rate increased from 4·19 events (95% CI 3·83–4·57) per 1000 person-years of follow-up in those with no INSTI exposure to a peak incidence rate of 8·46 events (6·58–10·71) per 1000 person-years at more than 0 months to 6 months of INSTI exposure, and then gradually decreased, returning to rates similar to among those with no INSTI exposure after more than 24 months of exposure (figure 3A). After adjusting for potential cardiovascular disease confounders, the adjusted incidence rate ratio (aIRR) of cardiovascular disease events remained significantly higher with more than 0 months to 6 months of INSTI exposure than among those with 0 months of exposure (aIRR 1·85 [95% CI 1·44–2·39]; figure 3B). The aIRR remained elevated at more than 6 months to 12 months of

exposure (1·19 [0·84–1·68]) and at more than 12 months to 24 months of exposure (1·46 [1·13–1·88]), although the associations were weaker than within the first 6 months of exposure. After 24 months of exposure, aIRRs decreased to levels similar to those when there was no INSTI exposure (figure 3B; table 2).

Although we did not have the statistical power to do adjusted analyses of each event comprising the composite endpoint, the crude incidence rate for myocardial infarctions, strokes, and invasive cardiovascular procedures was consistent with the primary analysis (data not shown). Moreover, because only 34 (15%) of 228 strokes were caused by cerebral haemorrhages, we could not meaningful separate ischaemic and haemorrhagic strokes.

Fitting CD4 cell count, BMI, hypertension, diabetes, chronic kidney disease, and dyslipidaemia as time-updated variables yielded results consistent with the primary analysis, as was the case when adding time-updated platelet counts to the model (table 2). Additionally, all sensitivity analyses gave consistent results with the primary analysis (table 2). We found no evidence suggesting that the association between INSTI exposure and cardiovascular disease differed according to baseline cardiovascular disease risk score or age group ($p_{interaction}$=0·27 for both), indicating that the association was similar in both individuals at high and low estimated cardiovascular disease risk and younger and older individuals. Likewise, the association was similar before and after Jan 1, 2014 ($p_{interaction}$=0·63), and for men and women ($p_{interaction}$=0·28).

In a post-hoc analysis, we found no interaction between INSTI exposure and ART treatment experience at baseline ($p_{interaction}$=0·18).

In an exploratory, post-hoc analysis of the effect of immunological and virological status when initiating INSTI, we found no difference between those with a good, poor, or intermediate immunological and virological markers on cardiovascular disease risk during first 6 months after starting an INSTI (p=0·20).

Discussion

To our knowledge, this is the first assessment of INSTI exposure and cardiovascular disease events to use data derived from a large and multinational cohort of people living with HIV seen in routine clinical care, with prospectively collected data and rigorously defined and centrally adjudicated endpoints. After accounting for cardiovascular disease risk factors, we observed that INSTI use in the first 6 months of exposure was associated with an almost two-times greater cardiovascular disease incidence than no INSTI exposure. Although the association was relatively weaker after the initial 6 months, the association persisted until 24 months of exposure, after which the incidence decreased to levels similar to those of individuals with no INSTI exposure. Our findings were consistent across a wide range of prespecified and post-hoc sensitivity

	Overall (n=29 340)	Cardiovascular disease event (n=748)	No cardiovascular disease event (n=28 592)
Gender*			
Female	7478 (25·5%)	93 (12·4%)	7385 (25·8%)
Male	21 818 (74·4%)	655 (87·6%)	21 163 (74·0%)
Age, years	44·3 (36·2–51·3)	53·4 (47·5–61·5)	44·0 (36·0–51·0)
Race and ethnicity			
White	20 419 (69·6%)	611 (81·7%)	19 808 (69·3%)
Black	2983 (10·2%)	20 (2·7%)	2963 (10·4%)
Other†	1267 (4·3%)	15 (2·0%)	1252 (4·4%)
Unknown	4671 (15·9%)	102 (13·6%)	4569 (16·0)
Geographical region			
West Europe	12 810 (43·7%)	443 (59·2%)	12 370 (43·3%)
South Europe and Argentina	6626 (22·6%)	140 (18·7%)	6486 (22·7%)
North Europe and Australia	7069 (24·1%)	129 (17·2%)	6940 (24·3%)
East Europe	2832 (9·7%)	36 (4·8%)	2796 (9·8%)
Risk of HIV acquisition			
Men who have sex with men	13 229 (45·1%)	362 (48·4%)	12 867 (45·0%)
Intravenous drug use	3993 (13·6%)	117 (15·6%)	3876 (13·6%)
Heterosexual sex	10 253 (34·9%)	216 (28·9%)	10 037 (35·1%)
Other	654 (2·2%)	15 (2·0%)	639 (2·2%)
Unknown	1211 (4·1%)	38 (5·1%)	1173 (4·1%)
CD4 count, cells per μL	524·0 (357·0–715·0)	554·0 (388·5–752·0)	523·0 (355·8–714·0)
Platelet count, cells per nL	200 (134–248)	213 (165–260)	200 (133–248)
CD4 nadir, cells per μL			
<200	11 925 (40·6%)	398 (53·2%)	11 527 (40·3%)
200 to <350	8757 (29·8%)	202 (27·0%)	8555 (29·9%)
350 to <500	4325 (14·7%)	74 (9·9%)	4251 (14·9%)
≥500	4333 (14·8%)	74 (9·9%)	4259 (14·9%)
Previous AIDS-defining disease			
Yes	5785 (19·7%)	221 (29·5%)	5564 (19·5%)
No	21 960 (74·8%)	504 (67·4%)	21 456 (75·0%)
Unknown	1595 (5·4%)	23 (3·1%)	1572 (5·5%)
ART treatment status			
ART naive	7172 (24·4%)	58 (7·8%)	7114 (24·9%)
ART experienced, viral load <200 copies per mL	19 951 (68·0%)	647 (86·5%)	19 304 (67·5%)
ART experienced, viral load ≥200 copies per mL	2217 (7·6%)	43 (5·7%)	2174 (7·6%)
BMI, kg/m²			
<18·5	873 (3·0%)	18 (2·4%)	855 (3·0%)
18·5 to <25	11 321 (38·6%)	335 (44·8%)	10 986 (38·4%)
25 to <30	1547 (5·3%)	51 (6·8%)	1496 (5·2%)
≥30	5159 (17·6%)	162 (21·7%)	4997 (17·5%)
Unknown	10 440 (35·6%)	182 (24·3%)	10 258 (35·9%)
Smoking status			
Never	8207 (28·0%)	191 (25·5%)	8016 (28·0%)
Current	8196 (27·9%)	305 (40·8%)	7891 (27·6%)
Previous	2261 (7·7%)	90 (12·0%)	2171 (7·6%)
Unknown	10 676 (36·4%)	162 (21·7%)	10 514 (36·8%)

(Table 1 continues on next page)

	Overall (n=29 340)	Cardiovascular disease event (n=748)	No cardiovascular disease event (n=28 592)
(Continued from previous page)			
Hypertension‡			
Yes	5683 (19·4%)	330 (44·1%)	5353 (18·7%)
No	18 531 (63·2%)	363 (48·5%)	18 168 (63·5%)
Unknown	5126 (17·5%)	55 (7·4%)	5071 (17·7%)
Diabetes§			
Yes	1170 (4·0%)	99 (13·2%)	1071 (3·7%)
No	22 054 (75·2%)	589 (78·7%)	21 465 (75·1%)
Unknown	6116 (20·8%)	60 (8·0%)	6056 (21·2%)
Dyslipidaemia¶			
Yes	17 984 (61·3%)	633 (84·6%)	17 351 (60·7%)
No	3813 (13·0%)	38 (5·1%)	3775 (13·2%)
Unknown	7543 (25·7%)	77 (10·3%)	7466 (26·1%)
Chronic kidney disease‖			
Yes	541 (1·8%)	44 (5·9%)	497 (1·7%)
No	25 934 (88·4%)	692 (92·5%)	25 242 (88·3%)
Unknown	2865 (9·8%)	12 (1·6%)	2853 (10·0%)
Previous cardiovascular disease event**			
Yes	666 (2·3%)	94 (12·6%)	572 (2·0%)
No	25 809 (88·0%)	642 (85·8%)	25 167 (88·0%)
Unknown	2865 (9·8%)	12 (1·6%)	2853 (10·0%)

Data are n (%) or median (IQR). p values for comparison of baseline characteristics between the groups with and event and without an event were 0·01 for risk of HIV acquisition and <0·001 for all other categories. ART=antiretroviral therapy. BMI=body-mass index. HICDEP=HIV Cohorts Data Exchange Protocol. *44 individuals in the group that did not experience an event identified as transgender. †Refers to all non-White and Non-Black ethnicities, as categorised by HICDEP. ‡Defined as systolic blood pressure of >140 mm Hg, diastolic blood pressure of >90 mm Hg, or use of antihypertensive drugs. §Defined as a random blood glucose measurement of >11·1 mmol/L, glycated haemoglobin concentration of >48 mmol/mol, use of antidiabetic drugs, or a noted diagnosis of diabetes. ¶Defined as total cholesterol being >6·2 mmol/L, high-density lipoprotein cholesterol of <0·9 mmol/L, triglyceride concentration of >2·3 mmol/L, or use of lipid-lowering treatment. ‖Defined as two or more estimated glomerular filtration rate measurements of <60 mL/min per 1·73 m^2. **Defined as myocardial infarction, stroke, and invasive cardiovascular procedures (ie, coronary angioplasty or stenting, coronary bypass surgery, and carotid endarterectomy).

Table 1: **Baseline demographic and clinical characteristics, overall and stratified by occurrence of cardiovascular disease events during follow-up**

For **HICDEP categories** see https://hicdep.org/Wiki/v/10/pt/4/Table/88/FieldID/1104

analyses, with no evidence suggesting that the association between INSTI exposure and the incidence of cardiovascular disease differed according to underlying estimated cardiovascular disease risk strata, age group, sex, calendar time, or immunological or virological status.

Randomised clinical trials and observational studies, including the RESPOND cohort itself, have suggested an association between INSTI use and increase in BMI,[18–20] especially within the first 12 months of initiating ART, and potentially also with metabolic syndrome.[20] Therefore, because increased BMI is associated with cardiovascular disease, INSTI exposure could potentially increase cardiovascular disease risk over time. Conversely, we found a rapid increase in the incidence of cardiovascular disease shortly after INSTI initiation, which was no longer present beyond 24 months of exposure; a pattern of association different from that previously described for cumulative exposure to some protease inhibitors[7,8,13] and recent exposure to abacavir.[8,9] Nevertheless, the strength of the association, with an aIRR of 1·85 within the first 6 months of exposure, and 1·46 between more than 12 months to 24 months, were similar in magnitude to previous reports for both cumulative exposure boosted protease inhibitors and recent exposure to abacavir.[7,8] If the association is indeed causal, it could imply that cardiovascular disease develops quickly after initiation of INSTIs in individuals with a specific underlying vulnerability; however, unmeasured confounding might have affected our findings.

The increased likelihood of starting an INSTI in individuals with an increased estimated 5-year cardiovascular disease risk score indicates at least some degree of confounding by indication, with individuals at risk of cardiovascular disease preferentially starting an INSTI-based regimen. However, notably, the association between INSTI use and incident cardiovascular disease remained after adjusting for cardiovascular disease risk profiles, including use of abacavir and other antiretroviral drugs previously associated with cardiovascular disease. Furthermore, the association was similar for both individuals with high and low estimated 5-year cardiovascular disease risk, reflected by a non-significant interaction test, suggesting that the findings cannot alone be explained by confounding by indication. Nevertheless, the absence of such an interaction warrants a cautious interpretation because of the test's limited statistical power.

RESPOND's observational nature does not allow us to establish causality of the found association. However, we examined possible mediator effects in exploratory analyses, adjusting for any effects of time-updated BMI, hypertension, diabetes, dyslipidaemia, and chronic kidney disease. These adjustments showed no attenuation in the aIRR of cardiovascular disease events; therefore, none of these factors are likely to mediate this increased incidence rate, consistent with these factors leading to cardiovascular disease via slow development of atherosclerosis, and so would not account for the rapid increase in the incidence rate of cardiovascular disease seen here. Additionally, previous findings from RESPOND analyses examining incident dyslipidaemia[27] and hypertension with INSTI exposure[28] have not shown an increase in these events within a period that precedes or matches the increased incidence rate of cardiovascular disease seen here; however, the time of the event was not the main focus of those analyses. Nevertheless, here we focused on the potential association between cardiovascular disease and INSTI exposure more broadly, not restricting the population to those potentially experiencing weight gain. However, understanding the potential effects of INSTI-related weight gain is of increasing clinical interest. Therefore, future investigations from the RESPOND study will examine potential associations between weight gain, cardiovascular disease risk factors, and cardiovascular

disease incidence in greater detail for the population who have weight gain related to INSTIs.

Overall, the absence of an attenuated effect after adjusting for BMI and other known risk factors for cardiovascular disease suggests one of two possible explanations: either that we have not captured the risk factors for cardiovascular disease through which INSTIs act to increase cardiovascular disease adequately, or that the association is in fact not causal, and is due to unmeasured risk factors in the INSTI-exposed population. A third possible explanation for our findings is that INSTIs can increase rates of cardiovascular disease events via a different mechanism unrelated to known risk factors. Such an effect could be similar to drug-induced platelet hyper-reactivity, which has been suggested as the mechanism linking abacavir to cardiovascular disease,[12] or the antibody-mediated clot formation and thrombocytopenia seen in vaccine-induced immune thrombotic thrombocytopenia.[29] However, introducing time-updated platelet counts into our model did not affect the aIRR, although we cannot adequately address thrombocyte function and other potential pathways in this study. We encourage further examinations of the possible underlying mechanism for the associations observed here in mechanistic studies.

INSTIs can cause a rapid increase in CD4 cell count in individuals initiating treatment who have a low CD4 count. Therefore, increased occurrence of immune reconstitution-inflammatory syndrome, or a similar phenomenon, with immunological changes that could mimic symptoms of cardiovascular disease or even cause type II, non-atherosclerotic, myocardial infarctions could also be suspected to underlie our findings. However, RESPOND's clinical event definitions exclude all suspected type II myocardial infarctions and strokes due to other causes such as opportunistic infections and cancers. Moreover, in addition to the low number of ART-naive individuals included in our analyses, there was no apparent difference in the association seen in the first 6 months of exposure after stratification of individuals by CD4 cell count and viral load at the time of INSTI initiation and the association was seemingly similar for ART-naive and ART-experienced individuals, as shown by the non-significant interaction test. Additionally, adding time-updated CD4 cell count to our model did not affect the cardiovascular disease risk in any substantial way. Therefore, immune reconstitution-inflammatory syndrome or a related condition as an explanation seems unlikely, even though we did not assess CD4 to CD8 cell count ratios in these analyses because these data were not available for all participants at present.

If we had focused exclusively on INSTI exposure of more than 0 months to 6 months as a reference, lower cardiovascular disease rates after 24 months might have been suggested; however, such an interpretation is not without caveats. If confounding by indication explains the initial peak in incidence of cardiovascular events within more than 0 months to 6 months of INSTI exposure, a comparison with this group would be biased towards lower incidences at all subsequent timepoints. Moreover, to confirm a decrease at more than 24 months of exposure compared with more than 0 months to 6 months of exposure would require substantially longer follow-up than was available for these analysis to also rule out an increase in cardiovascular disease with long-term exposure beyond 3 years.

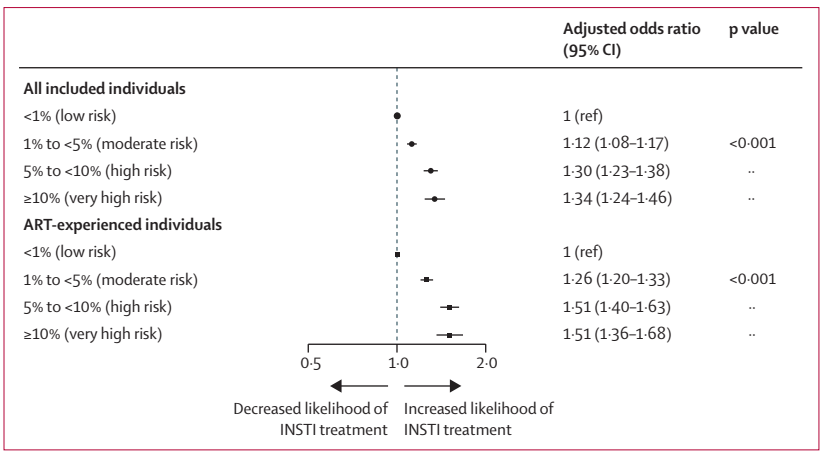

Figure 2: **Calendar time-adjusted likelihood of starting an INSTI, by D:A:D estimated 5-year cardiovascular disease risk score category**

ART=antiretroviral therapy. D:A:D=Data Collection on Adverse events of Anti-HIV Drugs. INSTI=integrase strand-transfer inhibitor.

Contrary to our findings here, no randomised clinical trials assessing INSTIs have reported a short-term increase in the incidence of cardiovascular disease.[14–17] Nevertheless, although randomised clinical trials are essential to determine ART efficacy and safety, they do generally not have the large sample size or duration of follow-up needed to uncover rarely occurring events such as cardiovascular disease. Although investigations of the occurrence of cardiovascular disease events with INSTI exposure are still scarce, a recently published US-based analysis showed no association between INSTI use and cardiovascular disease.[22] Nevertheless, the analysis had a retrospective design, did not assess incidence of cardiovascular disease stratified by exposure time, and excluded cardiovascular disease events occurring in the first 3 months of INSTI initiation. Therefore, an immediate effect might have been overlooked and further diluted by not accounting for events shortly after INSTI initiation. Additionally, a 2017 analysis from the US Veterans Health Administration cohort, assessing potential cardioprotective effects of atazanavir, reported hazard ratios of myocardial infarction and stroke that were lower for atazanavir than for INSTIs, in line with our findings.[21] However, the study period of the analysis spanned 2003–15 and the INSTI group was relatively small, including only a small number of individuals treated with second-generation INSTIs.[21]

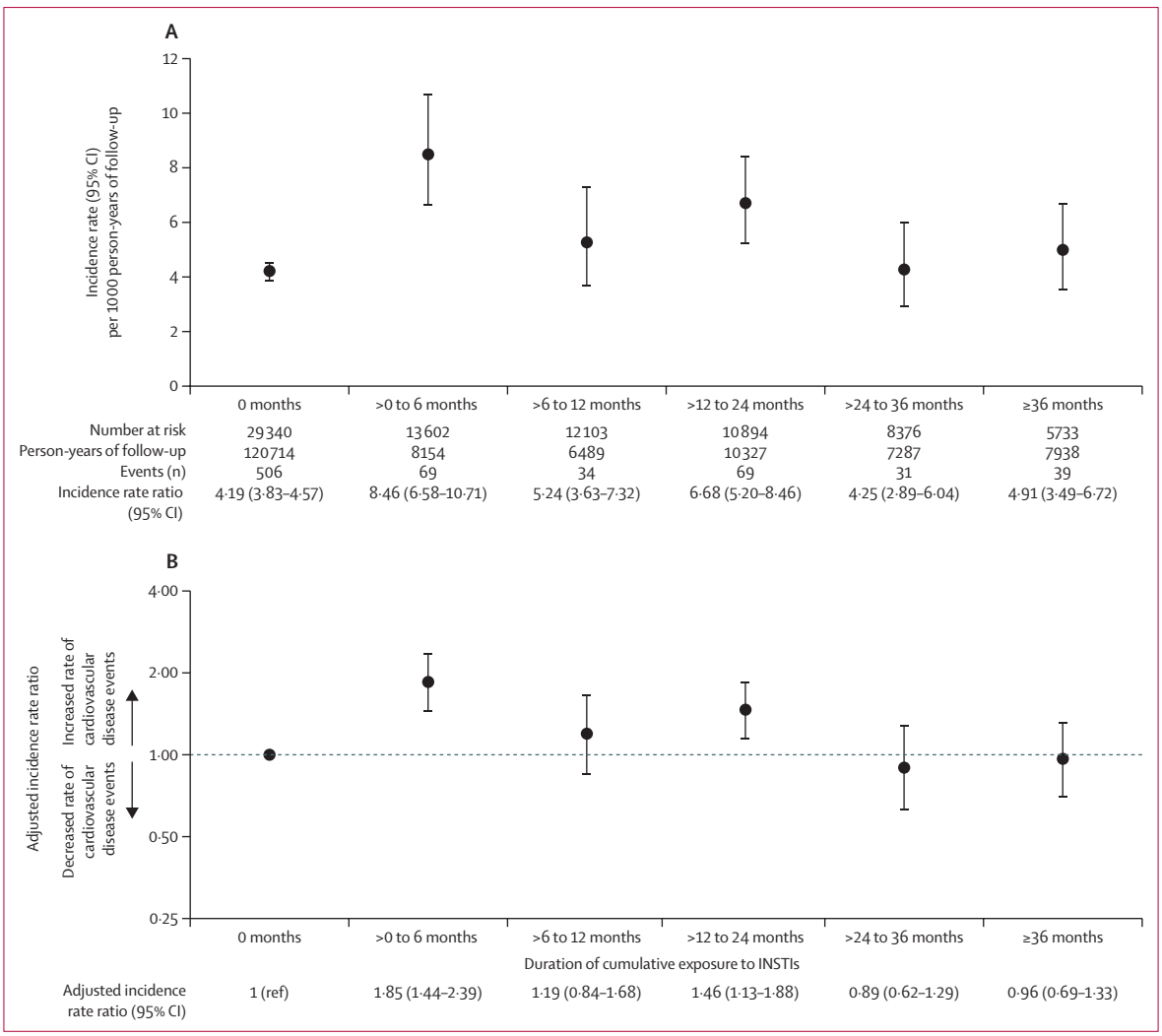

Figure 3: **Crude incidence rate of cardiovascular disease composite endpoint per 1000 person-years of follow-up (A) and adjusted incidence rate ratio of cardiovascular disease composite endpoint (B) by cumulative exposure to INSTIs**

Multivariable model adjusted for age, sex, race, geographical region, body-mass index, HIV acquisition risk, CD4 cell count, hypertension, diabetes, previous AIDS-defining conditions, previous cardiovascular disease, chronic kidney disease, dyslipidaemia, all fixed at baseline. Additionally, smoking and antiretroviral drugs previously associated with cardiovascular disease were included in the model as time-updated variables. INSTI=integrase strand-transfer inhibitor.

Our analysis has several limitations. First, because this is an observational study we cannot exclude the potential for residual confounders or channelling bias, as already discussed. We have applied the same methods developed and used in D:A:D pharmacovigilance analyses, adjusting for several potential confounders, and did numerous sensitivity analyses that gave consistent results, and interpreted the results of these cautiously and conservatively.[5–8] Nevertheless, propensity-score matching could have been used as an alternative to traditional regression analyses, although such methods also have their limitations. Second, we did not have adequate analytical power to restrict the analyses to only include ART-naive individuals or provide reliable estimates for individual INSTIs used at present, as also seen from post-hoc power calculations. Therefore, we assessed INSTIs collectively as a class for a combined population of ART-naive and ART-experienced individuals.

We acknowledge within-class differences in cardiovascular disease risk might exist among INSTIs, as shown for protease inhibitors,[13] and differences in cardiovascular disease risk assessments. However, our reporting of potential class effects used the same approach as earlier studies, including D:A:D, and allows for timely reporting of a potential safety signal of currently used ART, allowing for investigation in other studies and examination of potential mechanisms.[6–8] Assessments of the incidence of cardiovascular disease with cumulative use of individual INSTIs, stratified by ART experience, will be a focus area for RESPOND going forward and as follow-up time within the cohort

	0 months of exposure		>0 to 6 months of exposure		>6 to 12 months of exposure		>12 to 24 months of exposure		>24 to 36 months of exposure		>36 months of exposure		p values
	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	aIRR (95% CI)	Events (person-years of follow-up)	
Primary model (n=29 340)*	1 (ref)	506 (120 714)	1·85 (1·44–2·39)	69 (8154)	1·19 (0·84–1·68)	34 (6489)	1·46 (1·13–1·88)	69 (10 327)	0·89 (0·62–1·29)	31 (7287)	0·96 (0·69–1·33)	39 (7938)	<0·0001
Model with time-updated factors on the potential causal pathway (n=29 340)†	1 (ref)	506 (120 714)	1·92 (1·47–2·52)	69 (8154)	1·09 (0·74–1·61)	34 (6489)	1·27 (0·95–1·70)	69 (10 327)	0·81 (0·54–1·22)	31 (7287)	0·87 (0·61–1·26)	39 (7938)	<0·0001
Model with time-updated factors on the potential causal pathway and platelet count (n=29 340)‡	1 (ref)	506 (120 714)	1·93 (1·47–2·52)	69 (8154)	1·09 (0·74 –1·61)	34 (6489)	1·27 (0·95–1·70)	69 (10 327)	0·82 (0·54–1·23)	31 (7287)	0·88 (0·61–1·27)	39 (7938)	<0·0001
Model only adjusted for estimated D:A:D 5-year cardiovascular disease risk score (n=29 340)§	1 (ref)	506 (120 714)	2·07 (1·61–2·66)	69 (8154)	1·29 (0·91–1·83)	34 (6489)	1·61 (1·25–2·07)	69 (10 327)	1·00 (0·70–1·45)	31 (7287)	1·11 (0·80–1·53)	39 (7938)	<0·0001
Excluding individuals with previous cardiovascular disease events at baseline (n=28 674)¶	1 (ref)	445 (118 141)	1·83 (1·39–2·41)	60 (7976)	1·12 (0·77–1·63)	29 (6366)	1·36 (1·03–1·80)	58 (10 111)	0·86 (0·58–1·28)	27 (7141)	0·97 (0·69–1·38)	35 (7731)	0·0002
Excluding invasive cardiovascular procedures from the composite cardiovascular disease endpoint (n=29 340)‖	1 (ref)	353 (120 714)	1·77 (1·30–2·41)	47 (8154)	1·13 (0·74–1·73)	23 (6489)	1·55 (1·15–2·08)	52 (10 327)	0·73 (0·45–1·17)	18 (7287)	0·93 (0·63–1·38)	27 (7938)	0·0003
Including only individuals who switched or initiated a new ART regimen after Jan 1, 2012 (n=20 782)**	1 (ref)	118 (34 081)	1·76 (1·31–2·37)	73 (8609)	1·18 (0·82–1·71)	38 (6863)	1·41 (1·05–1·89)	74 (10 922)	0·98 (0·68–1·43)	37 (7730)	1·03 (0·72–1·46)	44 (8412)	0·0023
Including only centrally adjudicated cardiovascular disease events (n=21 188)††	1 (ref)	145 (40 886)	1·37 (0·89–2·12)	26 (4121)	1·30 (0·82–2·06)	22 (3744)	1·33 (0·93–1·90)	48 (7149)	0·93 (0·61–1·42)	27 (6006)	0·88 (0·59–1·31)	34 (7533)	0·22

aIRR=adjusted incidence rate ratio. BMI=body-mass index. D:A:D=Data Collection on Adverse events of Anti-HIV Drugs. INSTI=integrase strand-transfer inhibitor. *Adjusted for age, sex, race, geographical region, BMI, HIV acquisition risk, CD4 cell count, hypertension, diabetes, previous AIDS-defining conditions, previous cardiovascular disease event, chronic kidney disease, and dyslipidaemia, all fixed at baseline. Additionally, smoking and antiretroviral drugs previously associated with cardiovascular disease were included in the model as time-updated variables. †Adjusted as in primary model, with BMI, hypertension, diabetes, dyslipidaemia, chronic kidney disease, and CD4 cell count fitted as time-updated variables. ‡Adjusted as in primary model, with BMI, hypertension, diabetes, dyslipidaemia, chronic kidney disease, and CD4 cell count fitted as time-updated variables, and also time-updated platelet count. §Model adjusted only for D:A:D 5-year cardiovascular disease risk score at baseline. ¶Adjusted as in primary model, excluding individuals with previous cardiovascular disease event at baseline. ‖Adjusted as in primary model, excluding invasive cardiovascular procedures from the composite cardiovascular disease outcome. **Adjusted as in primary model, including only individuals who switched or initiated a new ART regimen after the RESPOND baseline, Jan 1, 2012. ††Adjusted as in primary model, including only centrally validated cardiovascular events; however, because the median time of cardiovascular disease event was before the validation period, the model included a substantially lower number of events (302 [40%] of 748 events were validated, of which 145 were in the no exposure group and 157 were in the exposure group) and had limited statistical power.

Table 2: **Adjusted incidence rate ratio of the cardiovascular disease composite endpoint by cumulative exposure to INSTIs, compared with no INSTI exposure, overall and in exploratory and sensitivity analyses**

increases. Finally, because RESPOND only includes individuals naive to INSTIs before Jan 1, 2012, we could not directly examine the association between cardiovascular disease and use of non-nucleotide reverse transcriptase inhibitors or boosted protease inhibitors with the same analytical approach because very few individuals within the cohort were naive to these two drug classes by Jan 1, 2012 (data not shown), and thus the statistical power was insufficient.

In summary, although we cannot exclude possible channelling bias and residual confounding, after accounting for cardiovascular disease risk factors, we found that INSTI exposure was associated with an aIRR of 1·85 for cardiovascular disease events in the first 6 months after INSTI initiation compared with no exposure. The association persisted up to 24 months of use, although with lower incidence rates than during the first 6 months of exposure. The association appeared similar in individuals with high and low estimated cardiovascular disease risk and across a wide range of sensitivity analyses. These early findings call for analyses in other large studies to verify our findings, and for the potential underlying mechanisms to be explored.

For the **RESPOND governance and procedures** see https://chip.dk/Portals/0/files/RESPOND/RESPOND%20governance%20and%20procedures_v6_2019SEP30.pdf?ver=2019-10-02-144419-230

For the **RESPOND data structure** see https://chip.dk/Research/Studies/RESPOND/Study-documents

For the **full RESPOND study group** see https://www.chip.dk/Research/Studies/RESPOND/Study-group

Contributors

BN, LG, AM, LR, and JDL proposed and developed the research question. BN wrote the first draft of the manuscript. LG did the statistical analyses. JDL, JMM, KG-P, GW, CS, SDW, FW, LP, AP-M, CMus, ACas, CP, AdM, JJV, AS, AVA, ACar, LB-M, HFG, FR, RZ, HG, LDR, CN, MvdV, MM, and CMuc contributed to the study design, interpretation of data, and revision of the manuscript. BN, LG, AM, and LR accessed and verified the underlying data. All authors have seen and contributed to the final version of the manuscript.

Declaration of interests

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Data sharing

The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk); for guidelines of how to submit research concepts see the RESPOND governance and procedures. The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to three people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are deidentified. The present RESPOND data structure and a list of all collected variables and their definitions can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat and Dorthe Raben, Director of Research Coordination (Dorthe.raben@regionh.dk).

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