Integrase strand-transfer inhibitor use and cardiovascular events in adults with HIV: an emulation of target trials in the HIV-CAUSAL Collaboration and the Antiretroviral Therapy Cohort Collaboration

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Summary

Background A recent observational study suggested that the risk of cardiovascular events could be higher among antiretroviral therapy (ART)-naive individuals with HIV who receive integrase strand-transfer inhibitor (INSTI)-based ART than among those who receive other ART regimens. We aimed to emulate target trials separately in ART-naive and ART-experienced individuals with HIV to examine the effect of using INSTI-based regimens versus other ART regimens on the 4-year risk of cardiovascular events.

Methods We used routinely recorded clinical data from 12 cohorts that collected information on cardiovascular events, BMI, and blood pressure from two international consortia of cohorts of people with HIV from Europe and North America. For the target trial in individuals who had previously never used ART (ie, ART-naive), eligibility criteria were aged 18 years or older, a detectable HIV-RNA measurement while ART-naive (>50 copies per mL), and no history of a cardiovascular event or cancer. Eligibility criteria for the target trial in those with previous use of non-INSTI-based ART (ie, ART-experienced) were the same except that individuals had to have been on at least one non-INSTI-based ART regimen and be virally suppressed (≤50 copies per mL). We assessed eligibility for both trials for each person-month between January, 2013, and January, 2023, and assigned individuals to the treatment strategy that was compatible with their data. We estimated the standardised 4-year risks of cardiovascular events (myocardial infarction, stroke, or invasive cardiovascular procedure) via pooled logistic regression models adjusting for time and baseline covariates. In per-protocol analyses, we censored individuals if they deviated from their assigned treatment strategy for more than 2 months and weighted uncensored individuals by the inverse of their time-varying probability of remaining uncensored. The denominator of the weight was estimated via a pooled logistic model that included baseline and time-varying covariates.

Findings The analysis in ART-naive individuals included 10 767 INSTI initiators and 8292 non-initiators of INSTI. There were 43 cardiovascular events in INSTI initiators (median follow-up of 29 months; IQR 15–45) and 52 in non-initiators (39 months; 18–47): standardised 4-year risks were 0·76% (95% CI 0·51 to 1·04) in INSTI initiators and 0·75% (0·54 to 0·98) in non-INSTI initiators; risk ratio 1·01 (0·57 to 1·57); risk difference 0·0089% (–0·43 to 0·36). The analysis in ART-experienced individuals included 7875 INSTI initiators and 373 965 non-initiators. There were 56 events in INSTI initiators (median follow-up 18 months; IQR 9–29) and 3103 events (808 unique) in non-INSTI initiators (26 months; 15–37) in non-initiators: standardised 4-year risks 1·41% (95% CI 0·88 to 2·03) in INSTI initiators and 1·48% (1·28 to 1·71) in non-initiators; risk ratio 0·95 (0·60 to 1·36); risk difference –0·068% (–0·60 to 0·52).

Interpretation We estimated that INSTI use did not result in a clinically meaningful increase of cardiovascular events in ART-naive and ART-experienced individuals with HIV.

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Introduction

Integrase strand-transfer inhibitors (INSTIs) are recommended as first-line antiretroviral therapy (ART) for people with HIV.[1–3] Dolutegravir is the preferred choice by WHO.[1] Randomised trials found that INSTI-based regimens are similar or superior[4–9] to other ART regimens in terms of effectiveness, safety, and potential for drug resistance. However, individuals who use INSTIs were also more likely to gain weight and develop metabolic complications than were those using protease inhibitors

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Research in context

Evidence before this study

We identified two observational studies in people with HIV by using the search term "cardiovascular disease and integrase strand-transfer inhibitors HIV" in PubMed from Jan 1, 2012 to May 10, 2023. No language restrictions were applied. A study in an administrative claims database in the USA found a 21% lower risk of cardiovascular events in individuals initiating integrase strand-transfer inhibitor (INSTI)-based regimens compared with those initiating other antiretroviral therapy (ART) combinations. The RESPOND collaboration from Europe and Australia found an 85% higher rate of cardiovascular events in individuals using INSTI-based regimens for up to 6 months compared with never users of an INSTI regimen. The incidence remained elevated until 24 months of use and then returned to levels similar to those in the never users. However, the results of this study are difficult to interpret because the design and analysis deviated from that of a target trial of INSTI use and cardiovascular events. A 2023 observational study in Switzerland did not find a difference in cardiovascular risk between initiators of INSTI-based and other regimens, but it was restricted to ART-naive individuals.

Added value of this study

Our observational analysis in two international consortia of people with HIV explicitly emulates a target trial, which prevents design biases. We conducted separate analyses in ART-naive and ART-experienced individuals. Our findings suggest that initiating INSTI regimens has little impact on cardiovascular risk. In ART-naive individuals, the 4-year risk ratio and risk difference were 1·01 (95% CI 0·57 to 1·57) and 0·0089% (–0·43 to 0·36). In ART-experienced individuals, the corresponding estimates were 0·95 (0·60 to 1·36) and –0·068% (–0·60% to 0·52%).

Implications of all the available evidence

When explicitly emulating a target trial, initiation of INSTI regimens was not found to affect cardiovascular outcomes in both people with HIV who started ART for the first time and those who were treatment experienced.

or non-nucleoside reverse transcriptase inhibitors in randomised trials[4,5,10–13] and observational studies.[14–16] Whether these increased risks of unfavourable metabolic outcomes translate to a higher risk of cardiovascular events in users of INSTIs compared with users of protease inhibitors[17] and non-nucleoside reverse transcriptase inhibitors[18,19] is unknown.

People with HIV have a higher risk of cardiovascular disease compared with the general population.[20–23] A recent randomised trial found that pitavastatin could prevent cardiovascular events in people with HIV and a low-to-moderate risk of cardiovascular disease.[24] As INSTI regimens are widely used, it is important to elucidate the cardiovascular effects of INSTI-based regimens to inform guidelines on use of ART and cardioprotective therapies. In the absence of randomised trials, this question needs to be addressed by analysing observational databases. A 2022 multinational observational study showed increased cardiovascular risk among users of INSTI regimens compared with users of other ART regimens.[25] However, the design of the study deviated from the design of a randomised trial, which could have introduced bias and complicated the interpretation of the results.[26] In contrast, an observational study in Switzerland did not find a difference in cardiovascular risk between initiators of INSTI-based and other regimens among ART-naive individuals.[27]

To examine the effect of initiation of INSTI regimens on the risk of cardiovascular events, we aimed to emulate target trials separately in individuals who had never previously used ART (ART-naive) and in individuals with previous use of non-INSTI-based ART (ART-experienced). The analyses were based on routinely recorded clinical data from two international consortia of cohorts of people with HIV from Europe and North America.

Methods

Study design and participants

The target trial emulation approach follows two steps: the specification of the protocol of the target trial, and the emulation of the target trial using the observational data. We first describe the protocol of the two target trials of interest, then describe the observational data, and then the procedures for emulating the target trials. We harmonised the method of the Swiss and the current study before publication of both.

The eligibility criteria for analysis of INSTI initiations in ART-naive people with HIV, over follow-up from January, 2013, to January, 2023, are age 18 years or older, an HIV-RNA measurement while ART-naive that had to be detectable (ie, >50 copies per mL), and no history of a cardiovascular event (ie, myocardial infarction, stroke, or invasive cardiovascular procedure) or cancer (appendix p 1). We selected 2013 as the initial year as this was when the US Federal Drug Administration approved the most used INSTI drug dolutegravir. We decided to exclude individuals with a previous cancer diagnosis as this would strongly influence treatment choice. The treatment strategies in the target trial were initiating an ART regimen containing an INSTI (individuals assigned to this strategy will be referred to as INSTI initiators) and initiating an ART regimen not containing an INSTI (individuals assigned to this strategy will be referred to as non-initiators of INSTI; this group includes users of a range of different ART regimens, including both protease inhibitors and non-nucleoside reverse transcriptase inhibitors). Eligible individuals would be randomly

assigned to a strategy and would be aware of their assignment. The outcome of interest would be a cardiovascular event (a composite outcome of myocardial infarction, stroke, or invasive cardiovascular procedure). Each eligible individual would be followed up from assignment (time zero) until the earliest date of a cardiovascular event, death, loss to follow-up (ie, 15 months without a new HIV-RNA measurement), administrative end of follow-up, or 4 years. The causal contrasts of interest are the intention-to-treat effect and the per-protocol effect.[28]

The intention-to-treat analysis estimates the 4-year risks (cumulative incidences) under each treatment strategy and compares them via ratios and differences. These risks can be estimated non-parametrically using the Kaplan-Meier method or parametrically by a pooled logistic regression model for the monthly risk of cardiovascular events that includes as covariates an indicator for treatment group, a flexible time-varying intercept, and product terms between treatment group and time. Baseline covariates whose distribution varies between groups (as quantified by large standardised mean differences)[29] are also included and the risks are then standardised to these baseline covariates. Non-parametric bootstrapping with 500 samples is used to calculate 95% CIs. The per-protocol analysis is the same except that individuals are censored when they deviate from their assigned treatment strategy and individuals are weighted by a time-varying non-stabilised inverse probability weight to adjust for the potential selection bias due to such censoring. Each individual receives a monthly weight inversely proportional to the estimated probability of remaining uncensored, which is estimated via a pooled logistic regression model for the monthly risk of treatment changes that includes baseline and time-varying prognostic factors as covariates.

The eligibility criteria for analysis of INSTI initiations in ART-experienced people with HIV are the same as for the target trial in ART-naive individuals except that individuals had to have been on at least one non-INSTI based ART regimen and be virally suppressed (≤50 copies per mL) to ensure that individuals initiated INSTI regimens for reasons other than virological failure, which is associated with increased cardiovascular risk (appendix p 2).[20,30] The treatment strategies are initiating (ie, switching to) an ART regimen containing an INSTI (INSTI initiators) and staying on the non-INSTI ART regimen or initiating (ie, switching to) a different ART regimen not containing an INSTI (non-initiators of INSTI). The outcome, follow-up, causal contrasts, and statistical analyses were identical to those of the target trial in ART-naive individuals.

Procedures

We emulated the target trials using observational data from the HIV-CAUSAL Collaboration[31] and the Antiretroviral Therapy Cohort Collaboration (ART-CC),[32] two consortia of cohorts of people with HIV from Europe and North America that record routinely collected data from infectious disease clinics. For the present analysis, we analysed data from individuals with known age and sex in 12 cohorts that collected information on cardiovascular events, as well as BMI and blood pressure. The list of cohorts included in the analysis is shown in the appendix (p 3). We defined cardiovascular events based on diagnostic codes for myocardial infarction, stroke, or invasive cardiovascular procedure (ie, coronary angioplasty or stenting, coronary bypass surgery, and carotid endarterectomy) and cause of death (at least one cause of death related to acute myocardial infarction or stroke), based on either HIV Cohorts Data Exchange Protocol[33] or International Classification of Diseases 9 or 10 codes, with some variation in the definition for three of the 12 cohorts (appendix pp 3–4). Validation of events varied by cohort and is described in the appendix (pp 4–5). When more than one regimen was used in a month, we assigned the one with the longest duration in that month. We disregarded treatments that lasted less than 7 days.

For each trial, we identified eligible individuals in January, 2013, and assigned them to the treatment strategy that was compatible with their data (ie, initiation or no initiation of an INSTI-based regimen). To emulate a randomised assignment, we assumed that INSTI initiation was random within levels of measured baseline covariates and included them in the pooled logistic model for the outcome. For the target trial emulation in ART-naive individuals, the baseline covariates were: age (continuous or modelled using restricted cubic splines); sex (sex at birth and binary); mode of HIV acquisition (self-defined as sex between men, heterosexual contact, injection drug use, and other or unknown); cohort; CD4 count in cells per μL (continuous or modelled using restricted cubic splines), HIV-RNA viral load in copies per mL (continuous modelled using restricted cubic splines), history of AIDS diagnosis (yes or no), history of hepatitis C virus co-infection (ie, positive hepatitis C virus antibody or hepatitis C virus-RNA concentration more than the level of detection); hepatitis B virus co-infection (positive hepatitis B surface Ag or hepatitis B virus DNA test); BMI (overweight or obese [BMI >25 kg/m²]; yes, no, or missing); high total cholesterol (≥240 mg/dL or >6·18 mmol/L; yes, no, or missing); uncontrolled hypertension (defined from systolic and diastolic blood pressure measurements; yes (yes being systolic ≥130 mm Hg or diastolic ≥80 mm Hg), no, or missing; smoking status (currently smoking, previous smoker, never smoked, or missing); history of type 1 or type 2 diabetes (clinical diagnosis, glycated haemoglobin A_{1C} ≥6·5%, or use of antidiabetic drugs or insulin); chronic kidney disease (≥stage 3, estimated glomerular filtration rate of <60; yes, no, or missing); using abacavir at baseline (yes or no) and calendar month. Implausible values of these variables were set to missing (appendix p 5). For the

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See **Online** for appendix

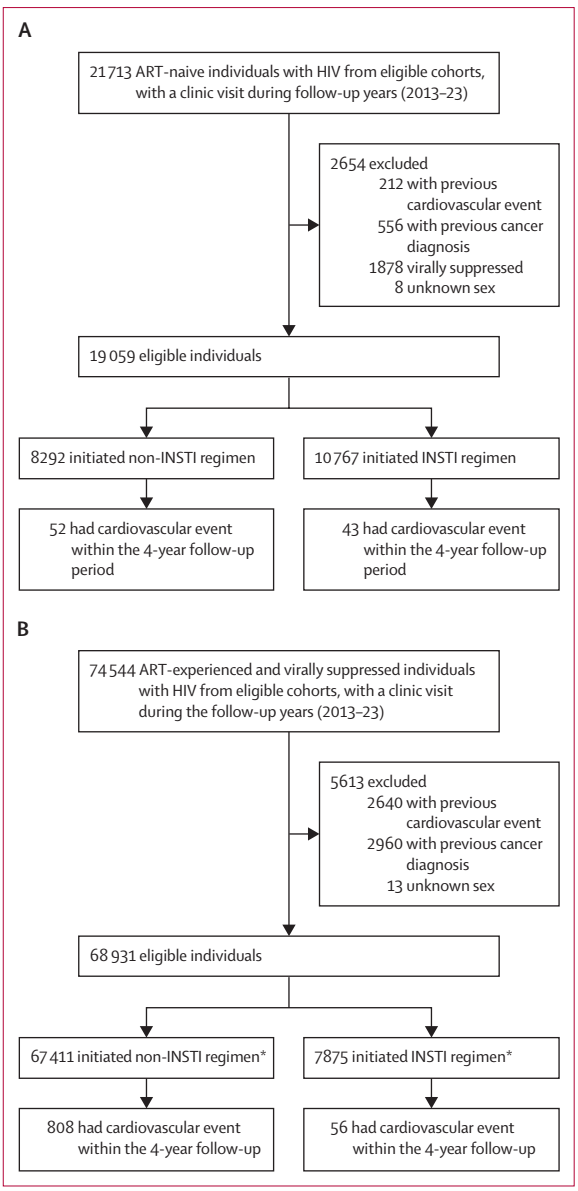

Figure 1: **Selection of individuals for the emulation of a target trial, 2013–23**
(A) ART-naive. (B) ART-experienced. ART=antiretroviral therapy. INSTI=integrase-strand transfer inhibitor. *Non-initiators of INSTI could be included as initiators in subsequent trials if they initiated INSTI and still met the eligibility criteria; therefore, the number of INSTI initiators and INSTI non-initiators exceeds the number of eligible individuals.

target trial in ART-experienced individuals, the baseline covariates were the same except that we did not include HIV-RNA (undetectable HIV viral load at baseline is one of the eligibility criteria) and we added time on ART (continuous and modelled using restricted cubic splines) and included abacavir within 6 months previously instead of only at baseline. The statistical analyses were the same as those described for the corresponding target trials, except that the process was repeated for each month until January, 2023 (ie, we emulated a sequence of 121 target trials with varying time zero).[26,34]

The per-protocol analyses for both emulated trials were the same as the intention-to-treat analyses except that we did not include covariates in the outcome model, we censored individuals if and when they deviated from their assigned treatment strategy for more than 2 months, and uncensored individuals received time-varying non-stabilised inverse-probability weights. The denominator of the weight in the ART-naive individuals was estimated via a pooled logistic model that included the baseline covariates of age, sex, mode of HIV acquisition, ethnicity, cohort, and ongoing abacavir use plus time-varying covariates CD4, HIV RNA, BMI, cholesterol, hypertension, smoking, diabetes, and chronic kidney disease. Baseline and time-varying covariates were the same in the analysis in ART-experienced individuals except that we included use of abacavir within 6 months before baseline instead of at baseline only and did not adjust for time-varying HIV RNA but for time-varying duration of ART. We truncated the weights at the 99th percentile to avoid undue influence of outliers.

Sensitivity analyses

We did several sensitivity analyses to assess the robustness of the results against small changes. We relaxed the definition of trial eligibility by requiring an HIV-RNA measurement in the 3 months before baseline instead of in the baseline month. We restricted initiation of INSTI to the top three most used regimens in the data (this covers 53% of INSTI initiators in the ART-naive population and 52% in the ART-experienced population; the top 5 regimens are described in the appendix [pp 5–6]). We restricted ART-naive INSTI initiators to those using regimens with dolutegravir or bictegravir as these are the INSTI drugs recommended for ART-naive people. We excluded two cohorts that did not provide data on cardiovascular procedures and cause of death and one that did not collect data on cardiovascular event type. We excluded one cohort from the analysis in ART-naive individuals because a similar analysis in ART-naive individuals was done in parallel within the cohort.[27] We excluded three cohorts that were also included in the previous multinational study. We adjusted for use of tenofovir alafenamide at baseline (due to its potential association with weight gain) and CD4 cell count nadir. We restricted follow-up to 2016 onwards. In the ART-experienced analysis, we additionally adjusted for cumulative months at baseline on antiretrovirals previously found to be associated with cardiovascular events (ie, indinavir, lopinavir, darunavir, and didanosine). Finally we restricted both analyses to men as the risk of cardiometabolic complications could differ between men and women.

We used SAS version 9.4 and R version 4.2.0 for the statistical analyses. This research was approved by the Institutional Review Board of the Harvard T H Chan School of Public Health. All participating cohorts received approval from their local Institutional Review Board.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Of 19 059 eligible individuals who were ART-naive, 10 767 started an INSTI regimen and 8292 started other ART regimens (figure 1). The number of people contributing to the sequential trials is shown in the appendix (p 3). Demographic and clinical characteristics in both groups were similar. Those who initiated INSTIs had a higher median HIV-RNA viral load and were more likely to use abacavir at baseline. Initiating INSTI-based regimens was more likely from 2015 onwards (table 1). Both INSTI initiators and non-initiators of INSTIs had the same median age (39 years) in the ART-naive group. The five most frequently used INSTI regimens in ART-naive people included drug combinations with dolutegravir, bictegravir, or elvitegravir. In non-initiators of INSTIs a wide range of regimens was used, including combinations with the

	ART-naive			ART-experienced		
	Initiators of INSTI: 10 767 person-trials (10 767 unique individuals)	Non-initiators of INSTI: 8292 person-trials (8292 unique individuals)	Standardised mean difference	Initiators of INSTI: 7875 person-trials (7875 unique individuals)	Non-initiators of INSTI: 373 965 person-trials (67 411 unique individuals)	Standardised mean difference
Sex	..	..	0·056	..	..	0·055
Male	9406 (87·4%)	7079 (85·4%)	..	6734 (85·5%)	312 694 (83·6%)	..
Female	1361 (12·6%)	1213 (14·6%)	..	1141 (14·5%)	61 271 (16·4%)	..
Median age, years	39 (30–49)	39 (31–49)	0·011	50 (41–59)	49 (40–57)	0·109
Ethnicity	..	..	0·056		..	0·260
White	4048 (37·6%)	2987 (36·0%)	..	3250 (41·3%)	147 934 (39·6%)	..
Black	1307 (12·1%)	977 (11·8%)	..	1896 (24·1%)	66 374 (17·7%)	..
Other	564 (5·2%)	376 (4·5%)	..	578 (7·3%)	21 583 (5·8%)	..
Unknown or missing	4848 (45·0%)	3952 (47·7%)	..	2151 (27·3%)	138 074 (36·9%)	..
Mode of HIV acquisition	..	..	0·124		..	0·341
Sex between men	5743 (53·3%)	4298 (51·8%)	..	2299 (29·2%)	141 273 (37·8%)	..
Heterosexual contact	2524 (23·4%)	2150 (25·9%)	..	1438 (18·3%)	89 475 (23·9%)	..
Injection drug use	259 (2·4%)	341 (4·1%)	..	321 (4·1%)	18 394 (4·9%)	..
Other or unknown	2241 (20·8%)	1503 (18·2%)	..	3817 (48·5%)	124 823 (33·4%)	..
Median CD4 count, cells per µl	354 (174–532)	339 (161–500)	0·069	629 (442–829)	620 (451–813)	0·007
Median HIV RNA, copies per mL	78 770 (18 698–327 520)	66 650 (16 030–275 305)	0·022	100% ≥50; part of eligibility criteria	100% ≥50; part of eligibility criteria	..
Median time since first started ART, years	..	..	..	7·2 (3·0–14)	6·1 (2·7–12·6)	0·117
AIDS diagnosis	901 (8·4%)	899 (10·8%)	0·085	956 (12·1%)	50 383 (13·5%)	0·041
Hepatitis C co-infection	568 (5·3%)	556 (6·7%)	0·056	1322 (16·8%)	57 256 (15·3%)	0·043
Hepatitis B co-infection	279 (2·6%)	266 (3·2%)	0·042	214 (2·7%)	12 328 (3·3%)	0·066
Overweight or obese (BMI >25 kg/m²)	..	..	0·027	..	..	0·114
No	4280 (39·8%)	3399 (41·0%)	..	3367 (42·8%)	170 484 (45·6%)	..
Yes	2373 (22·0%)	1777 (21·4%)	..	3658 (46·5%)	154 047 (41·2%)	..
Missing	4114 (38·2%)	3116 (37·6%)	..	850 (10·8%)	49 434 (13·2%)	..
Uncontrolled hypertension (systolic ≥130 mm Hg or diastolic ≥80 mm Hg)	..	..	0·032	..	..	0·125
No	3332 (30·9%)	2458 (29·6%)	..	3113 (39·5%)	136 620 (36·5%)	..
Yes	3944 (36·6%)	3047 (36·7%)	..	4277 (54·3%)	203 574 (54·4%)	..
Missing	3491 (32·4%)	2787 (33·6%)	..	485 (6·2%)	33 771 (9·0%)	..
High total cholesterol (≥240 mg/dL or >6·18 mmol/L)	..	..	0·108	..	..	0·038
No	8531 (79·2%)	6194 (74·7%)	..	6621 (84·1%)	322 086 (86·1%)	..
Yes	229 (2·1%)	219 (2·6%)	..	883 (11·2%)	37 738 (10·1%)	..
Missing	2007 (18·6%)	1879 (22·7%)	..	371 (4·7%)	14 141 (3·8%)	..

(Table 1 continues on next page)

	ART-naive			ART-experienced		
	Initiators of INSTI: 10 767 person-trials (10 767 unique individuals)	Non-initiators of INSTI: 8292 person-trials (8292 unique individuals)	Standardised mean difference	Initiators of INSTI: 7875 person-trials (7875 unique individuals)	Non-initiators of INSTI: 373 965 person-trials (67 411 unique individuals)	Standardised mean difference
(Continued from previous page)						
Smoking	..	..	0·059	..	..	0·186
Current smoker	2841 (26·3%)	2238 (27·0%)	..	2958 (37·6%)	139 516 (37·3%)	..
Previous smoker	383 (3·6%)	377 (4·5%)	..	1307 (16·6%)	52 222 (14·0%)	..
Never smoked	2832 (26·3%)	2038 (24·6%)	..	2573 (32·7%)	108 731 (29·1%)	..
Missing	4711 (43·8%)	3639 (43·9%)	..	1037 (13·2%)	73 496 (19·7%)	..
Diabetes (clinical diagnosis; A1C ≥6·5; use of antidiabetic drugs or insulin)	395 (3·7%)	272 (3·3%)	<0·001	946 (12·0%)	37 179 (9·9%)	<0·001
Chronic kidney disease ≥stage 3 (estimated glomerular filtration rate <60)	..	..	0·254	..	..	0·196
No	7367 (68·4%)	4718 (56·9%)	..	4000 (50·8%)	184 229 (49·3%)	..
Yes	203 (1·9%)	113 (1·4%)	..	635 (8·1%)	15 233 (4·1%)	..
Missing	3197 (29·7%)	3461 (41·7%)	..	3240 (41·1%)	174 503 (46·7%)	..
Abacavir use (baseline only in ART-naive and baseline or within 6 months previously in ART-experienced individuals)	2254 (20·9%)	501 (6·0%)	0·447	3360 (42·7%)	62 376 (16·7%)	0·524
Calendar year	..	..	0·984	..	..	0·692
2013	335 (3·1%)	2196 (26·5%)	..	480 (6·1%)	100 591 (26·9%)	..
2014	785 (7·3%)	1731 (20·9%)	..	1210 (15·4%)	96 254 (25·7%)	..
2015	1351 (12·5%)	1102 (13·3%)	..	2239 (28·4%)	82 465 (22·1%)	..
2016	1661 (15·4%)	695 (8·4%)	..	2445 (31·0%)	63 301 (16·9%)	..
2017	1838 (17·1%)	576 (6·9%)	..	655 (8·3%)	13 157 (3·5%)	..
2018	1570 (14·6%)	502 (6·1%)	..	370 (4·7%)	6799 (1·8%)	..
2019	1488 (13·8%)	507 (6·1%)	..	289 (3·7%)	4751 (1·3%)	..
2020	883 (8·2%)	382 (4·6%)	..	149 (1·9%)	3236 (0·9%)	..
2021	663 (6·2%)	442 (5·3%)	..	31 (0·4%)	2545 (0·7%)	..
2022	193 (1·8%)	155 (1·9%)	..	7 (0·1%)	861 (0·2%)	..
2023	0	4 (<0·1%)	..	0	5 (<0·1%)	..

Data are n (%) or median (IQR) unless otherwise stated. ART=antiretroviral therapy. INSTI=integrase strand-transfer inhibitor.

Table 1: **Baseline characteristics and standardised mean differences**

	4-year risk in ART-naive individuals (95% CI)				4-year risk in ART-experienced individuals (95% CI)			
	INSTI initiators	Non-initiators of INSTI	Risk ratio	Risk difference	INSTI initiators	Non-initiators of INSTI	Risk ratio	Risk difference
Unadjusted	0·62% (0·43 to 0·83)	0·96% (0·69 to 1·23)	0·65 (0·40 to 0·98)	−0·33% (−0·70 to 0·013)	1·41% (0·92 to 1·91)	1·50% (1·29 to 1·73)	0·94 (0·63 to 1·26)	−0·090% (−0·55 to 0·39)
Adjusted for age, sex, and cohort	0·65% (0·45 to 0·88)	0·82% (0·60 to 1·06)	0·80 (0·48 to 1·23)	−0·16% (−0·50 to 0·14)	1·59% (1·04 to 2·16)	1·47% (1·27 to 1·69)	1·08 (0·73 to 1·47)	0·12% (−0·39 to 0·66)
Adjusted for all baseline covariates*	0·76% (0·51 to 1·04)	0·75% (0·54 to 0·98)	1·01 (0·57 to 1·57)	0·0089% (−0·43 to 0·36)	1·41% (0·88 to 2·03)	1·48% (1·28 to 1·71)	0·95 (0·60 to 1·36)	−0·068% (−0·60 to 0·52)

ART=antiretroviral therapy. INSTI=integrase strand-transfer inhibitor. *Age, sex, mode of HIV acquisition, ethnicity, cohort, CD4 count, HIV RNA (only in ART-naive individuals), history of AIDS, hepatitis C virus, and hepatitis B virus, BMI >25 kg/m^2, high cholesterol, hypertension, smoking, abacavir use, diabetes, and chronic kidney disease (plus time on ART in ART-experienced individuals).

Table 2: **Estimated 4-year risk of cardiovascular events in ART-naive and ART-experienced individuals**

protease inhibitors darunavir or atazanavir and the non-nucleoside reverse transcrip tase inhibitors rilpivirine or efavirenz (appendix pp 5–6).

During follow-up among ART-naive individuals 1303 (12·1%) of 10 767 INSTI initiators discontinued INSTI use for more than 2 months and 2409 (29·1%) of

8292 non-initiators of INSTI started INSTI and stayed on it for more than 2 months. There were 43 cardiovascular events in the INSTI initiators group (median follow-up of 29 months; IQR 15–45) and 52 in the non-initiators group (39 months; 18–47). In the INSTI initiators, 25 (58%) of 43 events were strokes, 12 (28%) were myocardial infarctions, 3 (7%) were invasive cardiovascular procedures, and three (7%) were an unknown cardiovascular event type. In non-initiators of INSTI, 24 (46%) of 52 events were strokes, 17 (33%) were myocardial infarctions, eight (15%) were invasive cardiovascular procedures, and three (6%) were cardiovascular events of an unknown type. 253 people (1·3%) of 19 509 died during follow-up from causes other than cardiovascular events.

The 4-year cardiovascular event risk estimates were similar in INSTI initiators and non-initiators of INSTI, with the risk ratio centred around 1 and the risk difference around 0 (table 2). Figure 2 shows similar risks of a cardiovascular event over 4 years in both groups.

The results of the sensitivity analyses were overall consistent with the main results, although precision was low for subgroup analyses (appendix p 7). In the per-protocol analysis, there were 41 events in INSTI initiators over a median follow-up of 25 months (IQR 13–43) and 41 events in non-initiators over a median follow-up of 25 months (10–43). The 4-year risks were 0·60% (0·40 to 0·81) in INSTI initiators and 0·88% (0·48 to 1·35) in non-initiators of INSTI; risk ratio 0·69 (0·36 to 1·30) and risk difference –0·28% (–0·81 to 0·15).

Of 68 931 eligible ART-experienced individuals, 7875 started INSTI and 67 411 did not (figure 1). The latter contributed to 373 965 sequential trials. Initiators were less likely to have acquired HIV through sex between men, more likely to have taken abacavir within the previous 6 months, and more likely to have chronic kidney disease stage 3 or higher. INSTI initiations were more frequent in 2015 and 2016 (table 1). The five most frequently used INSTI regimens in ART-experienced people included three-drug combinations with dolutegravir, elvitegravir, or raltegravir. In the non-initiators of INSTI, combinations including the protease inhibitors darunavir or atazanavir and the non-nucleoside reverse transcriptase inhibitors rilpivirine, efavirenz, or nevirapine were used (appendix pp 5–6).

During follow-up of ART-experienced individuals, 1095 (13·9%) of 7875 initiators discontinued INSTI use for more than 2 months at a time and 17 800 (26·4%) of 67 411 non-initiators started INSTI and stayed on it for more than 2 months. There were 56 events (median follow-up 18 months; IQR 9–29) in initiators and 3103 events contributed by repeated trials with 808 unique events (26 months; 15–37) in non-initiators of INSTI in the intention-to-treat analysis. In INSTI initiators, 26 (46%) of 56 events were strokes, 18 (32%) were myocardial infarctions, and 12 (21%) were invasive cardiovascular procedures. In non-initiators of INSTI, 336 (42%) of 808 events were strokes, 314 (39%) were myocardial infarctions, 126 (16%) were invasive cardiovascular procedures, and 32 (4%) were cardiovascular events of an unknown type. 1306 (1·9%) of 68 931 individuals died during follow-up from causes other than cardiovascular events.

The 4-year cardiovascular event risk estimates were very similar in INSTI initiators and non-initiators of INSTI, with the risk ratio centred around 1 and the risk difference around 0 (table 2; figure 2).

The results of the sensitivity analyses were overall consistent with the main results. However, precision was low for the analysis restricting follow-up to 2016 onwards (appendix p 7). In the per-protocol analysis, there were 52 events and 2655 events (695 unique) in INSTI initiators and non-initiators of INSTI across a median follow-up of 16 months (IQR 7–26) and 22 months (12–34). The 4-year risks were 1·21% (0·80 to 1·77) in INSTI initiators and 1·34% (1·12 to 1·60) in non-initiators

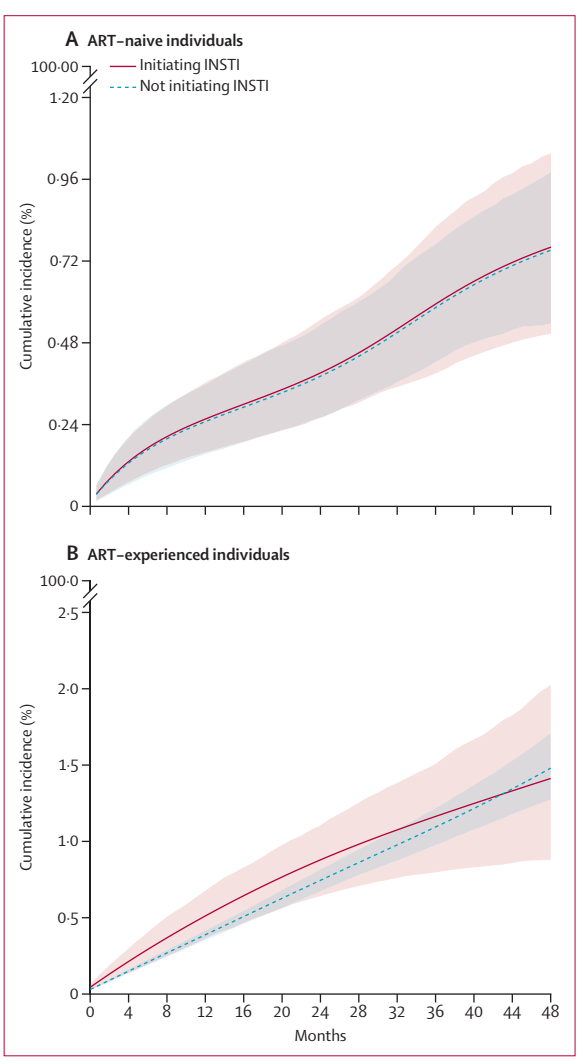

Figure 2: **Estimated cumulative incidence of cardiovascular events**
(A) ART-naive. (B) ART-experienced individuals. Standardised by covariates. ART=antiretroviral therapy. INSTI=integrase-strand transfer inhibitor.

of INSTI; risk ratio 0·90 (0·58 to 1·33) and risk difference –0·13% (–0·60 to 0·42).

Discussion

Using data from observational cohorts of people with HIV, we emulated target trials to estimate the effect of INSTI-based ART regimens on cardiovascular events. Our estimates suggest that initiation of INSTI does not substantially increase cardiovascular risk across 4 years with 4-year risk ratios centred around 1 and risk differences centred around 0 in both ART-naive and ART-experienced individuals. The upper limit of the 95% CI for the risk difference corresponds to an absolute increase in 4-year risk in INSTI initiators of only 0·36% in ART-naive individuals and 0·52% in ART-experienced individuals, which is unlikely to be a clinically meaningful difference. Overall, the risk of cardiovascular events was higher in ART-experienced compared with ART-naive individuals, which would be expected due to the ART-experienced population being older and having a higher prevalence of cardiovascular risk factors.

Our observational analysis explicitly emulates that of a randomised trial, which prevents design biases, and we conducted separate analyses in ART-experienced and ART-naive individuals.

In contrast, two previous observational studies did not specify a target trial, which makes directly comparing the estimates difficult. An observational study identified ART-naive individuals in the MarketScan database of US commercially insured and Medicaid covered adults between 2008 and 2015.[35] This study found a similar risk of cardiovascular events in individuals who were on a stable INSTI-based regimen compared with those on other ART combinations[35] although, under applying some form of inverse-probability weighting and censoring, the hazard ratio for INSTI versus no INSTI was less than 1. The RESPOND observational study,[25] which triggered our own assessment, found that the rate of cardiovascular disease events was increased in the first 24 months after INSTI initiation and then decreased to levels similar to those individuals never exposed to INSTI (cardiovascular event rate in those with 0–6 months of exposure was increased about two-fold compared with those with 0 months of exposure and gradually decreased after that). These findings, however, are difficult to interpret because the design and analysis deviated from that of a target trial of INSTI use and cardiovascular events. Specifically, individuals were assigned to treatment groups defined by the observed duration of INSTI use before and after the start of follow-up; also, because data were extracted retrospectively for at least 5 years, individuals who could have died from a cardiovascular event were excluded by design.

Our analyses and that of the Swiss HIV Cohort Study, which used an explicit target trial emulation approach, found little evidence of differences in cardiovascular risk between initiators of INSTI and of other ART regimens among previously ART-naive individuals.[27] Our analysis also found little evidence of cardiovascular risk differences in ART-experienced individuals.

Our study has several potential limitations. First, as in all observational studies, there could be unmeasured confounding. However, like previous observational studies, we adjusted for known demographic and clinical factors that could affect both INSTI use and cardiovascular events, including sex, age, smoking, BMI, blood pressure, and cholesterol levels. Second, because most cohorts capture routine care data from HIV or infectious disease clinics some cardiovascular events might not have been documented. The absolute risk of cardiovascular events in our study was lower than in the Swiss study (risks at 4 years 0·99% in INSTI initiators and 1·56% in non-initiators of INSTI) for ART-naive individuals but similar to the one in the RESPOND study (a risk of 2·5% across a median follow-up of 6·2 years implies a 4-year risk of 1·61% under a constant rate, similar to our estimates of 1·41% and 1·48% in initiators and non-initiators of INSTI, respectively) for ART-experienced individuals. Third, we could not precisely assess the impact of specific INSTI drugs on cardiovascular events, but analyses studying the three most used INSTI regimens and restricting initiators to users of dolutegravir or bictegravir in the ART-naive analysis yielded results consistent with the main analysis, although somewhat imprecise.

In conclusion, the findings of our observational study suggest that the use of INSTI regimens does not result in a clinically meaningful increase of cardiovascular events in people with HIV either when starting ART or among those who are treatment-experienced.

Contributors

SMR, MAH, SL, and BS contributed to the conception of the study. SMR, MAH, and SL contributed to the study design. SL, GT, LW, AvS, MvdV, MBK, JY, IJ, Ad'AM, ATa, LM, LT, MJG, BS, ACJ, and CTR contributed to the data acquisition. SMR and RWL contributed to the statistical analysis (both accessed and verified the data). SMR drafted the original Article. All authors contributed to the data interpretation, reviewing of the Article, critical revision of the Article for important intellectual content, and had final approval of the submitted Article.

Declaration of interests

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Data sharing

Data sharing agreements between the individual cohorts and HIV-CAUSAL and the Antiretroviral Therapy Cohort Collaboration prevent us from sharing the study data with third parties. Investigators interested in accessing these data should contact the individual cohorts, details of which are given in the appendix (pp 3–4).

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