Integrase strand-transfer inhibitor use and cardiovascular events in adults with HIV: An emulation of target trials in the HIV-CAUSAL and ART-CC Collaborations

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Research in context

Evidence before this study

We identified two observational studies in persons with HIV by using the search term "cardiovascular disease and integrase strand-transfer inhibitors HIV" in PubMed from January 1, 2012 to May 10, 2023. A study in an administrative claims database in the United States 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 a 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 rate 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 recent 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-naïve individuals.

Added value of this study

Our observational analysis in two international consortia of persons with HIV explicitly emulates a target trial, which prevents design biases. We conducted separate analyses in ART-naïve and ART-experienced individuals. Our findings suggest that initiating INSTI regimens has little impact on cardiovascular risk. In ART-naïve individuals, the 4-year risk ratio and risk difference were 1.01 (95% confidence interval: 0.57, 1.57) and 0.0089% (-0.43, 0.36). In ART-experienced individuals, the corresponding estimates were 0.95 (0.60, 1.36) and -0.068% (-0.60%, 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 persons with HIV who start ART for the first time and those who are treatment-experienced.

Abstract

Background

A recent observational study suggested that the risk of cardiovascular events may be higher among persons with HIV who receive integrase strand-transfer inhibitor (INSTI)-based antiretroviral therapy (ART) than among those who receive other ART regimens.

Methods

We used routinely recorded clinical data from two international consortia of cohorts of persons with HIV from Europe and North America to examine the effect of using INSTI-based regimens vs. other ART regimens (including those based on protease inhibitors and non-nucleoside reverse transcriptase inhibitors) on the 4-year risk of cardiovascular events. We emulated target trials separately in individuals who had never used ART (ART-naïve) and those with prior use of non-INSTI-based ART (ART-experienced), assessing trial eligibility for each person-month between January 2013 and January 2023. We estimated the standardized 4-year risks of cardiovascular events 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 >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-naïve individuals included 10,767 INSTI initiators and 8,292 non-initiators with similar clinical characteristics. The standardized 4-year risks (95% CI) of a cardiovascular event were 0.76% (0.51,1.04) (43 events) in INSTI initiators and 0.75% (0.54,0.98) (52 events) in non-INSTI initiators (risk ratio (RR) 1.01 (0.57,1.57); risk difference (RD) 0.0089% (-0.43,0.36)). The analysis in ART-experienced individuals included 7,875 INSTI initiators and 373,965 non-initiators with similar characteristics. Standardized 4-year risks were 1.41% (0.88,2.03) (56 events) and 1.48% (1.28,1.71) (3,103 events, 808 unique) (RR 0.95 (0.60,1.36); RD -0.068% (-0.60,0.52)). Results from per-protocol analyses were consistent with the main results.

Interpretation

We found that INSTI use has little impact on cardiovascular risk in ART-naïve and ART-experienced individuals.

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National Institute of Allergy and Infectious Diseases; National Institute on Alcohol Abuse and Alcoholism.

Introduction

Integrase strand-transfer inhibitors (INSTIs) are recommended as first-line antiretroviral therapy (ART) for persons with HIV[1,2,3]. Dolutegravir is the preferred choice by WHO[1]. Randomized trials found that INSTI-based regimens are similar or superior[4,5,6,7,8,9] to other ART regimens in terms of effectiveness, safety, and potential for drug resistance. However, individuals who use INSTIs were also found to be more likely to gain weight and develop metabolic complications compared with those using protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) in randomized trials[4,5,10,11,12,13] and observational studies[14,15,16]. It is unknown whether these increased risks of unfavorable metabolic outcomes translate to a higher risk of cardiovascular events in users of INSTIs compared to users of PIs[17] and NNRTIs[18,19].

As INSTI regimens are widely used and because of the higher risk of cardiovascular disease in persons with HIV compared with the general population[20,21,22,23], it is important to determine whether INSTI-based regimens affect cardiovascular risk. In the absence of randomized trials, this question needs to be addressed by analyzing observational databases. Recently, a multinational observational study reported increased cardiovascular risk among users of INSTI regimes compared with users of other ART regimes[24]. However, the design of the study deviated from the design of a randomized trial which may introduce bias and complicate the interpretation of the results[25]. 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-naïve individuals.[26]

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

Methods

The target trial emulation approach follows two steps: 1) the specification of the protocol of the target trial, and 2) 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 harmonized the methodology of the Swiss and the current study before publication of both.

Specification of a target trial in ART-naïve persons with HIV

Appendix I Table 1 outlines the protocol of the target trial in ART-naïve persons with HIV. The eligibility criteria over follow-up from 2013-2023 are age ≥18 years, an HIV-RNA measurement while ART-naïve that had to be detectable (>50 copies/ml) and no history of a cardiovascular event (myocardial infarction, stroke, or invasive cardiovascular procedure) or cancer. We selected 2013 as the initial year as this was when the US Federal Drug Administration approved the most commonly used INSTI drug dolutegravir. We decided to exclude individuals with a prior cancer diagnosis as this would strongly influence treatment choice. The treatment strategies in the target trial are (1) initiating an ART regimen containing an INSTI (individuals assigned to this strategy will be referred to as "INSTI initiators"), and 2) 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 PIs and NNRTIs). 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 (defined as a composite outcome of myocardial infarction, stroke, or invasive cardiovascular procedure). Each eligible individual would be followed from assignment (time zero) until the earliest date of a cardiovascular event, death, loss to follow-up (15 months without a new HIV-RNA measurement), administrative end of follow-up, or four years. The causal contrasts of interest are the intention-to-treat effect and the per-protocol effect[27].

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 may be estimated nonparametrically 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 standardized mean differences[28]) are also included and the risks are then standardized to these baseline covariates. Nonparametric bootstrapping with 500 samples is used to calculate 95% confidence intervals (CI). The per-protocol analysis is the same except that 1) individuals are censored if and when they deviate from their assigned treatment strategy, and 2) individuals are weighted by a time-varying nonstabilized 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.

Specification of a target trial in ART-experienced, INSTI-naïve persons with HIV

Appendix I Table 2 outlines the protocol of the target trial in ART-experienced individuals. The eligibility criteria are the same as for the target trial in ART-naïve individuals except that individuals had to have been on at least one non-INSTI based ART regimen and be virally suppressed (≤50 copies/ml) to ensure that individuals initiate INSTI regimens for reasons other than virological failure, which is associated with increased cardiovascular risk[20,29]. The treatment strategies are (1) initiating (i.e., switching to) an ART regimen containing an INSTI ("INSTI initiators"), and 2) staying on the current non-INSTI ART regimen or initiating (i.e., switching to) a different ART regimen not containing an INSTI ("non-initiators of INSTI"). The outcome, follow-up, causal contrasts and statistical analyses are identical to those of the target trial in ART-naïve individuals.

Observational data

We emulated the above target trials using observational data from the HIV-CAUSAL Collaboration[30] and the Antiretroviral Therapy Cohort Collaboration (ART-CC)[31], two consortia of cohorts of persons with HIV from Europe and North America that record routinely collected data from infectious disease clinics. For the present analysis, we analyzed data from individuals with known age and sex in 12 cohorts that collected information on cardiovascular events, as well as body mass index (BMI), and blood pressure. The list of cohorts included in the analysis is shown in Appendix II. We defined cardiovascular events based on diagnostic codes for myocardial infarction, stroke, or invasive cardiovascular procedure (coronary angioplasty/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 (HICDEP)[32] or ICD-9 or ICD-10 codes, with some variation in the definition for three out of the 12 cohorts (see Appendix III for details). Validation of events varied by cohort and is described in Appendix IV. 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 seven days.

Emulation of the target trials

For each trial, we identified eligible individuals in January 2013 and assigned them to the treatment strategy that was compatible with their data (initiation or no initiation of an INSTI-based regime). To emulate a randomized 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-naïve individuals, the baseline covariates were: age (continuous, modelled using restricted cubic splines); sex (sex at birth, binary); mode of HIV acquisition (self-defined; sex between men, heterosexual contact, injection drug use, other/unknown); cohort; CD4 count in cells/μl (continuous, modelled using restricted cubic splines), HIV-RNA viral load in copies/ml (continuous, modelled using restricted cubic splines), history of AIDS diagnosis (yes/no), history of hepatitis C virus (HCV) co-infection (positive HCV antibody or HCV-RNA above the level of detection); hepatitis B virus (HBV) co-infection (positive Hepatitis B Surface Ag or HBV DNA test); body mass index (BMI) (overweight or obese (BMI>25): yes/no/missing); high total cholesterol (≥240 mg/dL or >6.18 mmol/L: yes/no/missing); uncontrolled hypertension (defined from systolic and diastolic blood pressure measurements: no; yes (systolic ≥130 or diastolic ≥80 mmHg); missing; smoking status (currently smoking, ex-smoker, never smoker, missing); history of type 1 or 2 diabetes (clinical diagnosis, hemoglobin A1C≥6.5, or use of antidiabetic drugs or insulin); chronic kidney disease (≥stage 3, estimated glomerular filtration rate (GFR)<60: yes/no/missing); using abacavir at baseline (yes/no) and calendar month. Implausible values of these variables were set to missing (see Appendix V). For the 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, 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, i.e., we emulated a sequence of 121 target trials with varying time zero[25,33].

The per-protocol analyses for both emulated trials were the same as the intention-to-treat analyses except that 1) we did not include covariates in the outcome model, 2) we censored individuals if and when they deviated from their assigned treatment strategy for more than two months, and 3) uncensored individuals received time-varying nonstabilized inverse-probability (IP) weights. The denominator of the weight in the ART-naïve individuals was estimated via a pooled logistic model that included the baseline covariates 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

In sensitivity analyses to assess the robustness of the results against small changes in the analysis: 1) we relaxed the definition of trial eligibility by requiring an HIV-RNA measurement in the 3-month period before baseline instead of in the baseline month; 2) we restricted initiation of INSTI to the top three most used regimens in the data (this covers 53% of INSTI initiators in the ART-naïve population and 52% in the ART-experienced population; the top 5 regimens are described in Appendix VI); 3) we restricted ART-naïve INSTI initiators to those using regimens with dolutegravir or bictegravir as these are the INSTI drugs currently recommended for ART-naïve persons; 4) 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; 5) we excluded one cohort, the Swiss HIV Cohort Study, from the analysis in ART-naïve individuals because a similar analysis in ART-naïve individuals was conducted in parallel within the cohort[26]; 6) we excluded three cohorts that were also included in the previous multinational study; 7) we additionally adjusted for use of tenofovir alafenamide at baseline (due to its potential association with weight gain) and CD4 count nadir; 8) we restricted follow-up to 2016 onwards; 9) in the ART-experienced analysis, we additionally adjusted for cumulative months at baseline on antiretrovirals previously been found to be associated with cardiovascular events (indinavir; lopinavir; darunavir; didanosine); and 10) we restricted both analyses to men as the risk of cardiometabolic complications may 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 (IRB) of the Harvard TH Chan School of Public Health. All participating cohorts received approval from their local IRB.

Role of the funding source

The funders played no role in the study.

Results

ART-naïve individuals

The analysis in ART-naïve individuals included 10,767 INSTI initiators and 8,292 non-initiators of INSTI. Figure 1a shows the selection process of individuals into the study. The number of persons contributing to the sequential trials is shown in Appendix II. Demographic and clinical characteristics in both groups were very similar but with INSTI initiators having a somewhat higher median HIV-RNA viral load and being 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 INSTI had the same median age (39 years). The five most frequently used INSTI regimens in ART-naïve persons included 3-drug combinations with dolutegravir, bictegravir or elvitegravir. In non-initiators of INSTI a wide range of regimens was used, including combinations with the PIs darunavir or atazanavir and the NNRTIs rilpivirine or efavirenz (Appendix VI).

During follow-up, 12% of initiators discontinued INSTI use for more than two months and 29% of non-initiators started INSTI and stayed on it for more than two months. There were 43 and 52 cardiovascular events in the INSTI initiators and non-initiators of INSTI over a median follow-up (interquartile range (IQR)) of 29 (15-45) and 39 (18-47) months. In INSTI initiators, 15 events (58%) were strokes, 12 (28%) were myocardial infarctions, 3 (7%) invasive cardiovascular procedures and 3 (7%) of an unknown cardiovascular event type. In non-initiators of INSTI, 24 events (46%) were strokes, 17 (33%) myocardial infarctions, 8 (15%) invasive cardiovascular procedures, and 3 (6%) cardiovascular events of an unknown type. A total of 253 persons (1.3%) 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 centered around 1 and the risk difference around 0 (table 2). Figure 2a 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 VII). In the per-protocol analysis, there were 41 events in INSTI initiators over a median (IQR) follow-up of 25 (13-43) and 41 events in non-initiators over a median follow-up of 25 (10-43) months. The 4-year risks were 0.60% (0.40, 0.81) in INSTI initiators and 0.88% (0.48, 1.35) in non-initiators of INSTI; risk ratio: 0.69 (0.36, 1.30) and risk difference -0.28% (-0.81, 0.15).

ART-experienced individuals

The analysis in ART-experienced individuals included 7,875 INSTI initiators (unique individuals) and 373,965 non-initiators of INSTI (67,411 unique individuals). Figure 1b shows the inclusion process of ART-experienced individuals. Again, INSTI initiators and non-initiators of INSTI had similar demographic and clinical characteristics, but with initiators being somewhat less likely to have acquired HIV through sex between men, more likely to have taken abacavir within the previous 6 months and to have chronic kidney disease stage ≥ 3. INSTI initiations were more frequent in 2015 and 2016 (table 1). The five most frequently used INSTI regimens in ART-experienced persons included 3-drug combinations with dolutegravir, elvitegravir or raltegravir. In the non-initiators of INSTI, combinations including the PIs darunavir or atazanavir and the NNRTIs rilpivirine, efavirenz or nevirapine were used (Appendix VI).

During follow-up, 14% of initiators discontinued INSTI use for more than 2 months at a time and 26% of non-initiators started INSTI and stayed on it for more than two months. There were 56 events over 18 months median follow-up (IQR 9-29) in initiators and 3,103 events (total events contributed by repeated trials; 808 unique events) over 26 (15-37) months in non-initiators of INSTI in the ITT analysis. In INSTI initiators, 26 events (46%) were strokes, 18 (32%) were myocardial infarctions and 12 (21%) invasive cardiovascular procedures. In non-initiators of INSTI, 336 events (42%) were strokes, 314 (39%) myocardial infarctions, 126 (16%) invasive cardiovascular procedures, and 32 (4%) cardiovascular events of an unknown type. A total of 1,306 persons (1.9%) 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 centered around 1 and the risk difference around 0 (table 2). Figure 2b 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. However, precision was low for the analysis restricting follow-up to 2016 onwards (Appendix VII). In the per-protocol analysis, there were 52 events and 2,655 (695 unique) events in INSTI initiators and non-initiators of INSTI over a median (IQR) follow-up of 16 (7-26) and 22 (12-34) months. The 4-year risks were 1.21% (0.80, 1.77) in INSTI initiators and 1.34% (1.12, 1.60) in non-initiators of INSTI; risk ratio: 0.90 (0.58, 1.33); risk difference: -0.13% (-0.60, 0.42).

Discussion

Using data from observational cohorts of persons with HIV, we emulated target trials to estimate the effect of INSTI-based ART regimes on cardiovascular events. Our estimates suggest that initiation of INSTI does not substantially increase cardiovascular risk over 4 years with 4-year risk ratios centered around 1 and risk differences centered around 0 in both ART-naïve and ART-experienced persons. The upper limit of the 95% confidence interval for the risk difference corresponds to an absolute increase in 4-year risk in INSTI initiators of only 0.36% in ART-naïve 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 to ART-naïve 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 randomized trial, which prevents design biases, and we conducted separate analyses in ART-experienced and ART-naïve individuals. In contrast, two previous observational studies did not specify a target trial, which makes it difficult to directly compare the estimates. An observational study identified ART-naïve individuals in the MarketScan database of US commercially insured and Medicaid covered adults between 2008 and 2015[34]. This study found a similar risk of cardiovascular events in individuals who were on a stable INSTI-based regime compared with those on other ART combinations[34] though, under applying some form of IP weighting and censoring, the hazard ratio for INSTI vs. no INSTI was under 1. The RESPOND observational study, 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 never exposed to INSTI (cardiovascular event rate in those with 0-6 months of exposure was increased about two-fold compared to those with 0 months of exposure and gradually decreased after that)[24]. 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 five years, individuals who may 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-naïve individuals[26]. 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 may be unmeasured confounding. However, like previous observational studies, we adjusted for known demographic and clinical factors that may 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 may 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-naïve individuals but similar to the one in the RESPOND study (a risk of 2.5% over 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) 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-naïve 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 persons with HIV either when starting ART or among those who are treatment experienced.

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Author contributions

Conception: Sophia Rein, Miguel Hernan, Sara Lodi, Bernard Surial; Study design: Sophia Rein, Miguel Hernan, Sara Lodi; Acquisition of data: Sara Lodi, Giota Touloumi, Linda Wittkop, Ard van Sighem, Marc van der Valk, Marina Klein, Jim Young, Inma Jarrin, Antonella D'Arminio Monforte, Alessandro Tavelli, Laurence Meyer, Laurent Tran, John Gill, Bernard Surial, Amy Justice, Christopher Rentsch; Statistical analysis: Sophia Rein and Roger Logan (both accessed and verified the data); Interpretation of the data: All authors; Drafted the article:

Sophia Rein; Review of the article: All authors; Critical revision for important intellectual content: All authors; Final approval of the submitted version: all authors.

Declaration of interests

SR, RL and SI report NIH grants paid to their institution during the conduct of the study; SL reports grants from the NIH and the Providence/Boston Center for AIDS Research; MAH reports grants from the NIH and personal honoraria from Cytel, ProPublica and ADIA Lab; JACS reports grants from the NIH and UK NIHR; AP received grants from the Wellcome Trust, BMGF, NIH and UK NIHR and payments from Bill & Melinda Gates Foundation outside of the study;FB reports grants and personal fees from Gilead Sciences, outside the submitted work; IJ reports payments from Gilead Sciences, GESIDA and ViiV Healthcare; MJG participated on advisory boards of Merck, Gilead and ViiV; MBK has received grants and honoraria from ViiV Healthcare, AbbVie and Gilead; LM reports grants from ANRS-MIE INSERM paid to her institution; RL received grants from CIHR, Alberta Innovates and the University of Calgary outside of the study; PR reports grants from Gilead Sciences, ViiV Healthcare and Merck&Co; CAS and MvdV report separate grants and honoraria from Gilead Sciences, ViiV Healthcare and MSD outside of the presented work; BS reports personal fees from Gilead Sciences and ViiV Healthcare; GT received grants from Gilead Sciences, UCL and EU and National funds; AvS reports grants from the Dutch Ministry of Health, Welfare and Sport and the European Centre for Disease Prevention and Control (ECDC); LW received grants from ANRS MIE.

Data sharing statement

Data sharing agreements between the individual cohorts and HIV-CAUSAL/ART-CC 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.

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Table 1. Baseline characteristics and standardized differences (SMD) among ART-naïve and ART-experienced individuals included in the emulation of a target trial of INSTI initiation, HIV-CAUSAL and ART-CC Collaborations 2013-2022

	ART-naïve			**ART-experienced**		
Characteristics	**Initiators of INSTI – 10,767 person-trials (10,767 unique individuals)**	**Non-Initiators of INSTI – 8,292 person-trials (8,292 unique individuals)**	**SMD**	**Initiators of INSTI – 7,875 person trials (7,875 unique individuals)**	**Non-initiators of INSTI – 373,965 person trials (67,411 unique individuals)**	**SMD**
Sex			0.056			0.055
Male	9,406 (87%)	7,079 (85%)		6,734 (86%)	312,694 (84%)	
Female	1,361 (13%)	1,213 (15%)		1,141 (14%)	61,271 (16%)	
Median age, in years (IQR)	39 (30-49)	39 (31-49)	0.011	50 (41-59)	49 (40-57)	0.11
Ethnicity			0.056			0.26
White	4,048 (38%)	2,987 (36%)		3,250 (41%)	147,934 (40%)	
Black	1,307 (12%)	977 (12%)		1,896 (24%)	66,374 (18%)	
Other	564 (5.2%)	376 (4.5%)		578 (7.3%)	21,583 (5.8%)	
Unknown/missing	4,848 (45%)	3,952 (48%)		2,151 (27%)	138,074 (37%)	
Mode of HIV acquisition			0.12			0.34
Sex between men	5,743 (53%)	4,298 (52%)		2,299 (29%)	141,273 (38%)	
Heterosexual contact	2,524 (23%)	2,150 (26%)		1,438 (18%)	89,475 (24%)	
IDU	259 (2.4%)	341 (4.1%)		321 (4.1%)	18,394 (4.9%)	
Other/unknown	2,241 (21%)	1,503 (18%)		3,817 (48%)	124,823 (33%)	
Median CD4 count, in cells/µl (IQR)	354 (174-532)	339 (161-500)	0.069	629 (442-829)	620 (451-813)	0.007
Median HIV RNA, in copies/ml (IQR)	78770 (18698-327520)	66650 (16030-275305)	0.022	100% ≤50; part of eligibility criteria	100% ≤50; part of eligibility criteria	-
Median time since first started ART in years (IQR)	-	-	-	7.2 (3.0-14)	6.1 (2.7-12.6)	0.12
AIDS diagnosis	901 (8.4%)	899 (11%)	0.085	956 (12%)	50,383 (13%)	0.041
HCV co-infection	568 (5.3%)	556 (6.7%)	0.056	1,322 (17%)	57,256 (15%)	0.043
HBV co-infection	279 (2.6%)	266 (3.2%)	0.042	214 (2.7%)	12,328 (3.3%)	0.066

	ART-naïve			ART-experienced		
Characteristics	**Initiators of INSTI – 10,767 person-trials (10,767 unique individuals)**	**Non-Initiators of INSTI – 8,292 person-trials (8,292 unique individuals)**	**SMD**	**Initiators of INSTI – 7,875 person trials (7,875 unique individuals)**	**Non-initiators of INSTI – 373,965 person trials (67,411 unique individuals)**	**SMD**
Overweight or obese (BMI >25)			0.027			0.11
No	4,280 (40%)	3,399 (41%)		3,367 (43%)	170,484 (46%)	
Yes	2,373 (22%)	1,777 (21%)		3,658 (46%)	154,047 (41%)	
Missing	4,114 (38%)	3,116 (38%)		850 (11%)	49,434 (13%)	
Uncontrolled hypertension (systolic ≥130 or diastolic ≥80 mmHg)			0.032			0.13
No	3,332 (31%)	2,458 (30%)		3,113 (40%)	136,620 (37%)	
Yes						
Missing	3,944 (37%)	3,047 (37%)		4,277 (54%)	203,574 (54%)	
	3,491 (32%)	2,787 (34%)		485 (6.2%)	33,771 (9.0%)	
High total cholesterol (≥240 mg/dL or >6.18 mmol/L)			0.11			0.038
No	8,531 (79%)	6,194 (75%)		6,621 (84%)	322,086 (86%)	
Yes	229 (2.1%)	219 (2.6%)		883 (11%)	37,738 (10%)	
Missing	2,007 (19%)	1,879 (23%)		371 (4.7%)	14,141 (3.8%)	
Smoking			0.059			0.19
Current smoker	2,841 (26%)	2,238 (27%)		2,958 (38%)	139,516 (37%)	
Ex-smoker	383 (3.6%)	377 (4.5%)		1,307 (17%)	52,222 (14%)	
Never smoker	2,832 (26%)	2,038 (25%)		2,573 (33%)	108,731 (29%)	
Missing	4,711 (44%)	3,639 (44%)		1,037 (13%)	73,496 (20%)	
Diabetes mellitus (clinical diagnosis; A1C≥6.5; use of antidiabetic drugs or insulin) (%)	395 (3.7%)	272 (3.3%)	<0.001	946 (12%)	37,179 (10%)	<0.001
Chronic kidney disease ≥stage 3 (eGFR<60)			0.25			0.20
No	7,367 (68%)	4,718 (57%)		4,000 (51%)	184,229 (49%)	
Yes	203 (1.9%)	113 (1.4%)		635 (8.1%)	15,233 (4.1%)	

	ART-naïve			ART-experienced		
Characteristics	**Initiators of INSTI – 10,767 person-trials (10,767 unique individuals)**	**Non-Initiators of INSTI – 8,292 person-trials (8,292 unique individuals)**	**SMD**	**Initiators of INSTI – 7,875 person trials (7,875 unique individuals)**	**Non-initiators of INSTI – 373,965 person trials (67,411 unique individuals)**	**SMD**
Missing	3,197 (30%)	3,461 (42%)		3,240 (41%)	174,503 (47%)	
Abacavir use (baseline only in ART-naïve and baseline or within 6 months previously in ART-experienced)	2,254 (21%)	501 (6.0%)	0.45	3,360 (43%)	62,376 (17%)	0.52
Calendar year			0.98			0.69
2013	335 (3.1%)	2,196 (26%)		480 (6.1%)	100,591 (27%)	
2014	785 (7.3%)	1,731 (21%)		1,210 (15%)	96,254 (26%)	
2015	1,351 (13%)	1,102 (13%)		2,239 (28%)	82,465 (22%)	
2016	1,661 (15%)	695 (8.4%)		2,445 (31%)	63,301 (17%)	
2017	1,838 (17%)	576 (6.9%)		655 (8.3%)	13,157 (3.5%)	
2018	1,570 (15%)	502 (6.1%)		370 (4.7%)	6,799 (1.8%)	
2019	1,488 (14%)	507 (6.1%)		289 (3.7%)	4,751 (1.3%)	
2020	883 (8.2%)	382 (4.6%)		149 (1.9%)	3,236 (0.86%)	
2021	663 (6.2%)	442 (5.3%)		31 (0.39%)	2,545 (0.68%)	
2022	193 (1.7%)	155 (1.9%)		7 (0.089%)	861 (0.23%)	
2023	0 (0%)	4 (0.048%)		0 (0%)	5 (0.0013%)	

ART=antiretroviral therapy; HCV=Hepatitis C co-infection; HBV=Hepatitis B co-infection; BMI=body mass index; eGFR=estimated glomerular filtration rate; IDU=injection drug use; IQR=interquartile range; INSTI=integrase strand-transfer inhibitor; SMD=standardized mean difference

Table 2. Estimated 4-year risk of cardiovascular events in ART-naïve and ART-experienced individuals included in the emulation of a target trial of INSTI initiation, HIV-CAUSAL Collaboration 2013-2022

	4-year risk in ART-naïve individuals (95% CI)				**4-year risk in ART-experienced individuals (95% CI)**			
Model	**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, 0.83)	0.96 (0.69, 1.23)	0.65 (0.40, 0.98)	-0.33 (-0.70, -0.013)	1.41% (0.92, 1.91)	1.50% (1.29, 1.73)	0.94 (0.63, 1.26)	-0.090% (-0.55,0.39)
Adjusted for age, sex and cohort	0.65 (0.45, 0.88)	0.82 (0.60, 1.06)	0.80 (0.48, 1.23)	-0.16% (-0.50, 0.14)	1.59% (1.04, 2.16)	1.47% (1.27, 1.69)	1.08 (0.73, 1.47)	0.12% (-0.39,0.66)
Adjusted for all baseline covariates*	0.76 (0.51, 1.04)	0.75 (0.54, 0.98)	1.01 (0.57, 1.57)	0.0089% (-0.43, 0.36)	1.41% (0.88, 2.03)	1.48% (1.28, 1.71)	0.95 (0.60, 1.36)	-0.068% (-0.60,0.52)

*age, sex, mode of HIV acquisition, ethnicity, cohort, CD4, HIV RNA (only in ART-naïve individuals), history of AIDS, HCV/HBV, BMI>25, high cholesterol, hypertension, smoking, abacavir use, diabetes, chronic kidney disease (plus time on ART in ART-experienced individuals).

Figure 1. Selection of eligible ART-naïve and ART-experienced individuals for the emulation of a target trial of INSTI initiation, HIV-CAUSAL and ART-CC Collaborations 2013-2023

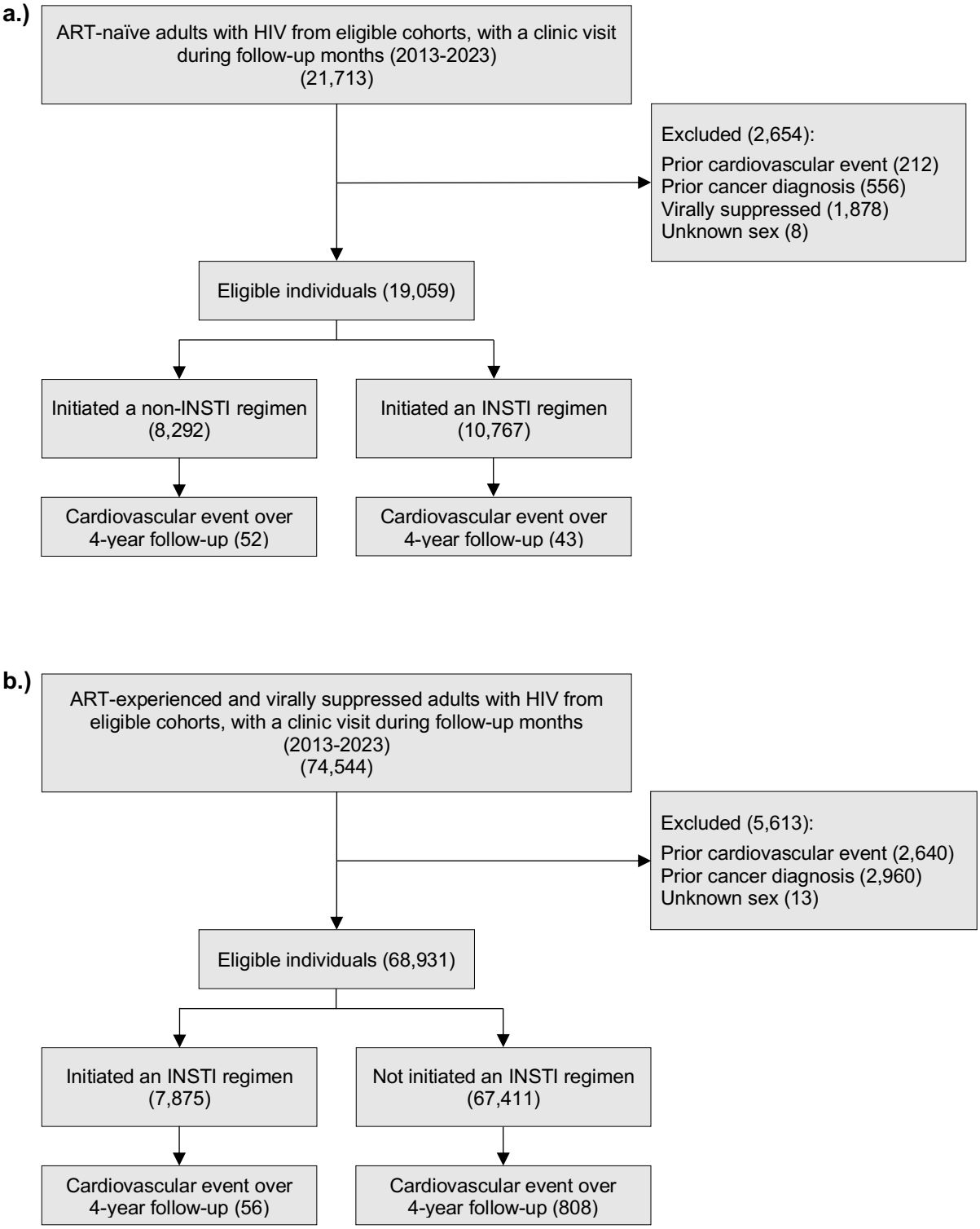

Figure 2. Estimated cumulative incidence over follow-up in ART-naïve and ART-experienced individuals included in the emulation of a target trial of INSTI initiation, HIV-CAUSAL and ART-CC Collaborations 2013-2023 (standardized by covariates)