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 antiretroviral therapy (ART)-naïve persons with HIV who receive integrase strand-transfer inhibitor (INSTI)-based ART than among those who receive other ART regimens. We emulated target trials separately in ART-naïve and ART-experienced persons with HIV 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.

Methods

We used routinely recorded clinical data from 12 cohorts that collected information on cardiovascular events, body mass index and blood pressure from two international consortia of cohorts of persons with HIV from Europe and North America. For the target trial in individuals who had previously never used ART (ART-naïve) eligibility criteria were: age ≥18 years, a detectable HIV-RNA measurement while ART-naïve (>50 copies/ml), no history of a cardiovascular event or cancer. Eligibility criteria for the target trial in those with prior use of non-INSTI-based ART (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/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 standardized 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 >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 estimated that INSTI use did not result in a clinically meaningful increase of cardiovascular events in ART-naïve 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 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].

Persons with HIV have a higher risk of cardiovascular disease compared with the general population[20,21,22,23]. A recent randomized trial found that pitavastatin may 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 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[25]. 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[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-naïve individuals[27].

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.

Study design and participants

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

Appendix I Table 1 (page 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[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 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[29]) 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 (page 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[20,30]. 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.

Procedures

Observational data

We emulated the above 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 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 (page 3). 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)[33] or ICD-9 or ICD-10 codes, with some variation in the definition for three out of the 12 cohorts (see Appendix III (pages 3-4) for details). Validation of events varied by cohort and is described in Appendix IV (pages 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 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, page 5). 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[26,34].

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, pages 5-6); 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[27]; 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

Figure 1a shows the selection process of individuals into the study. Of 19,059 eligible individuals who were ART-naive, 10,767 started INSTI and 8,292 did not. The number of persons contributing to the sequential trials is shown in Appendix II (page 3). Demographic and clinical characteristics in both groups were similar. INSTI initiators 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 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, pages 5-6).

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, page 7). 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

Figure 1b shows the inclusion process of ART-experienced individuals. Of 68,931 eligible individuals, 7,875 started INSTI and 67,411 did not. The latter contributed to 373,965 sequential trials. Again, INSTI initiators and non-initiators of INSTI had similar demographic and clinical characteristics. Initiators were 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, pages 5-6).

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, page 7). 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[35]. 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 [35] 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)[25]. 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[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 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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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. All other authors declare no competing interests.

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 (pages 3-4).

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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
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%)	

	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**
Yes Missing	3,944 (37%) 3,491 (32%)	3,047 (37%) 2,787 (34%)		4,277 (54%) 485 (6.2%)	203,574 (54%) 33,771 (9.0%)	
High total cholesterol (≥240 mg/dL or >6.18 mmol/L) No Yes Missing	 8,531 (79%) 229 (2.1%) 2,007 (19%)	 6,194 (75%) 219 (2.6%) 1,879 (23%)	0.11	 6,621 (84%) 883 (11%) 371 (4.7%)	 322,086 (86%) 37,738 (10%) 14,141 (3.8%)	0.038
Smoking Current smoker Ex-smoker Never smoker Missing	 2,841 (26%) 383 (3.6%) 2,832 (26%) 4,711 (44%)	 2,238 (27%) 377 (4.5%) 2,038 (25%) 3,639 (44%)	0.059	 2,958 (38%) 1,307 (17%) 2,573 (33%) 1,037 (13%)	 139,516 (37%) 52,222 (14%) 108,731 (29%) 73,496 (20%)	0.19
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) No Yes Missing	 7,367 (68%) 203 (1.9%) 3,197 (30%)	 4,718 (57%) 113 (1.4%) 3,461 (42%)	0.25	 4,000 (51%) 635 (8.1%) 3,240 (41%)	 184,229 (49%) 15,233 (4.1%) 174,503 (47%)	0.20
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 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023	 335 (3.1%) 785 (7.3%) 1,351 (13%) 1,661 (15%) 1,838 (17%) 1,570 (15%) 1,488 (14%) 883 (8.2%) 663 (6.2%) 193 (1.7%) 0 (0%)	 2,196 (26%) 1,731 (21%) 1,102 (13%) 695 (8.4%) 576 (6.9%) 502 (6.1%) 507 (6.1%) 382 (4.6%) 442 (5.3%) 155 (1.9%) 4 (0.048%)	0.98	 480 (6.1%) 1,210 (15%) 2,239 (28%) 2,445 (31%) 655 (8.3%) 370 (4.7%) 289 (3.7%) 149 (1.9%) 31 (0.39%) 7 (0.089%) 0 (0%)	 100,591 (27%) 96,254 (26%) 82,465 (22%) 63,301 (17%) 13,157 (3.5%) 6,799 (1.8%) 4,751 (1.3%) 3,236 (0.86%) 2,545 (0.68%) 861 (0.23%) 5 (0.0013%)	0.69

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

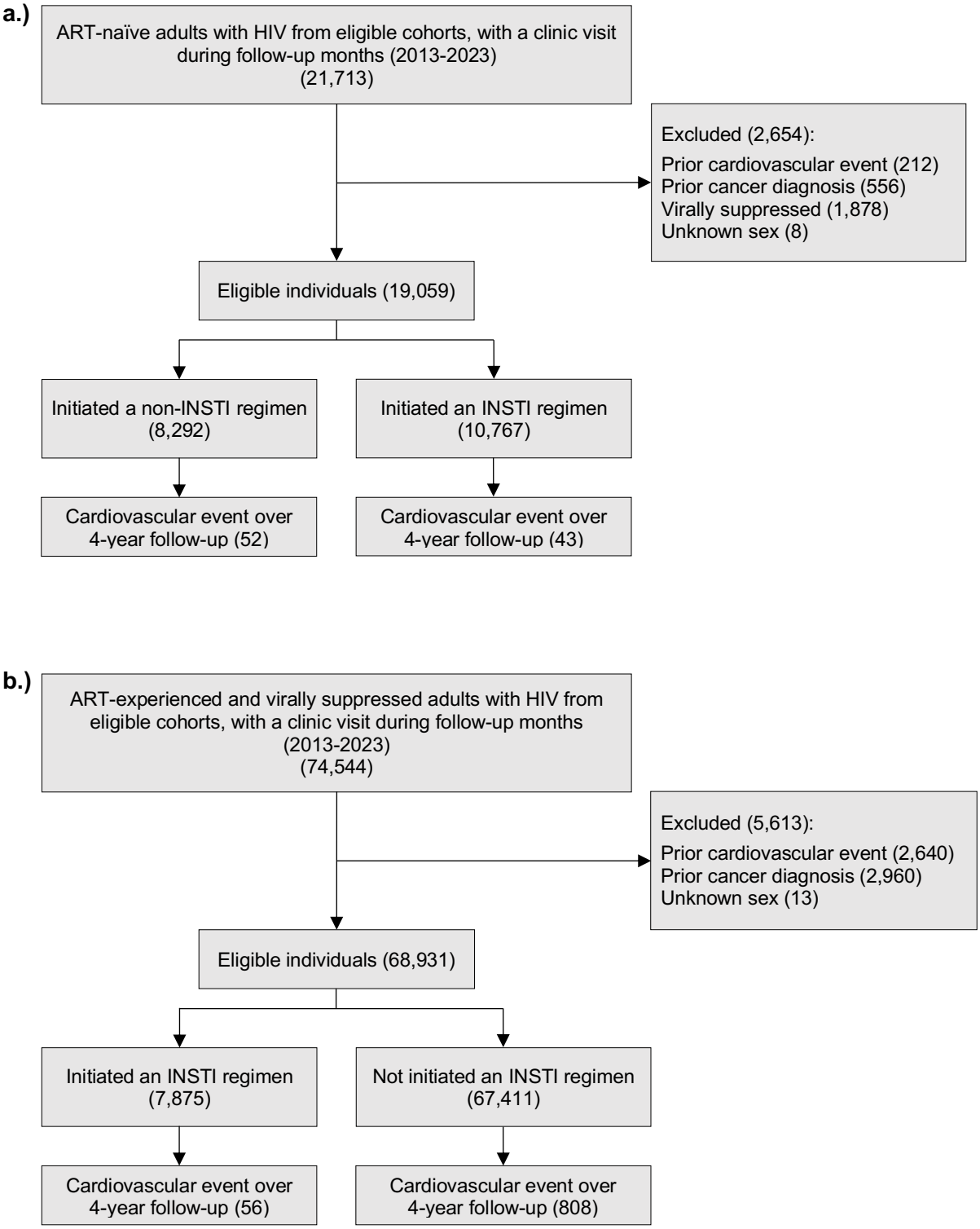
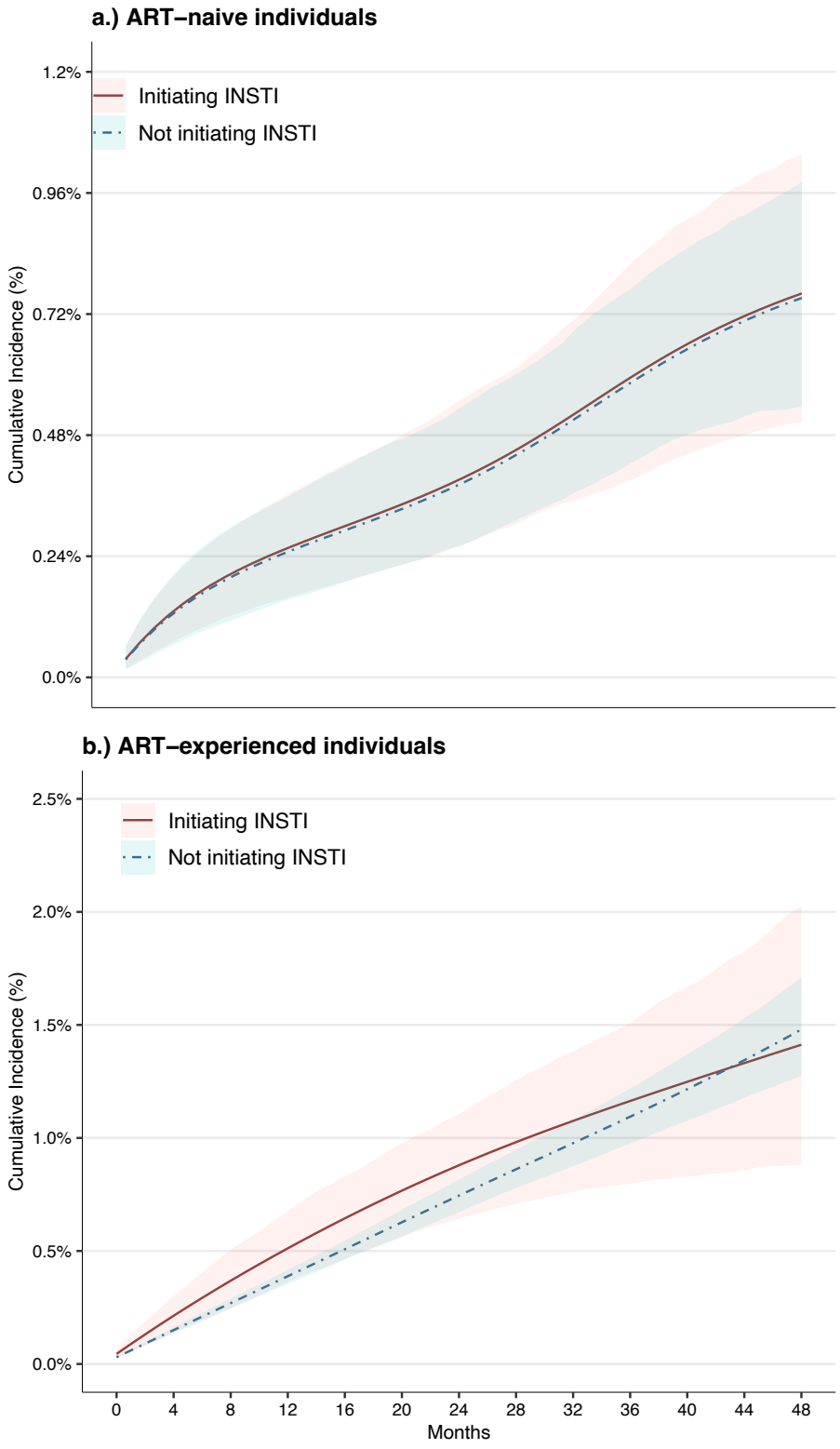


Figure 2. Estimated cumulative incidence over follow-up in ART-naïve and ART-experienced individuals included in the emulation of a target trial of INSTI initiation, HIV-CAUSAL and ART-CC Collaborations 2013-2023 (standardized by covariates)



Appendix

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Appendix I. Target trial emulation protocols

Table 1. Target trial protocol for analysis of INSTI initiations in ART-naïve persons with HIV

Component	Target trial	Emulated trial
Eligibility criteria	• Diagnosis of HIV infection • age 18 years or older • ART-naive • no known history of cardiovascular events or cancer	Same.
Treatment strategies	1. Initiate an ART regimen containing an INSTI 2. Initiate an ART regimen not containing an INSTI	Same.
Treatment assignment	Patients are randomly assigned and are aware of the strategy they are assigned to	Randomization is assumed conditional on baseline covariates: age, sex, mode of HIV acquisition, ethnicity, cohort, CD4 count, HIV RNA, history of AIDS, HCV/HBV co-infection, BMI, cholesterol, hypertension, smoking, diabetes, chronic kidney disease, abacavir use
Outcome	Cardiovascular event (myocardial infarction, stroke or invasive cardiovascular procedure)	Same.
Follow-up	Follow-up begins at assignment and ends when a patient experiences the outcome, death, loss to follow-up or at the end of the study, whichever occurs first	Same.
Causal estimands	• Intention-to-treat effect • Per-protocol effect	Observational analogs of both
Statistical analysis	• Intention-to-treat analysis: Comparison of 4-year risks in each treatment group; estimated via a hazards model. • Per-protocol analysis: Same but with adjustment for adherence via inverse probability weighting with baseline covariates age, sex, mode of HIV acquisition, ethnicity, cohort and abacavir use and time-varying covariates CD4 count, HIV RNA, BMI, cholesterol, hypertension, smoking, diabetes, chronic kidney disease	Same with sequential target trial emulation.

ART=antiretroviral therapy; BMI=body mass index; HCV=hepatitis C virus; HBV=hepatitis B virus; INSTI=integrase strand-transfer inhibitor

Table 2. Target trial protocol for analysis of INSTI initiations in ART-experienced persons with HIV

Component	Target trial	Emulated trial
Eligibility criteria	• Diagnosis of HIV infection • age 18 years or older • Currently on ART • no previous exposure to an INSTI • no known history of cardiovascular events or cancer • virologically suppressed (≤50 copies/ml)	Same.
Treatment strategies	1. Initiating an ART regimen containing an INSTI 2. Stay on current ART regimen or initiate different ART regimen not containing an INSTI	Same.
Treatment assignment	Patients are randomly assigned and are aware of the strategy they are assigned to	Randomization is assumed according to baseline covariates: age, sex, mode of HIV acquisition, ethnicity, cohort, time on ART, CD4 count, history of AIDS, HCV/HBV co-infection, BMI, cholesterol, hypertension, smoking, history of abacavir use, diabetes, chronic kidney disease
Outcome	Cardiovascular event (myocardial infarction, stroke or invasive cardiovascular procedure)	Same.
Follow-up	Follow-up begins at assignment and ends when a patient experiences the outcome, death, loss to follow-up or at administrative end of follow-up, whichever occurs first	Same.
Causal estimands	• Intention-to-treat effect • Per-protocol effect	Observational analogs of both
Statistical analysis	• Intention-to-treat analysis: Comparison of 4-year risks in each treatment group; estimated via a hazards model. • Per-protocol analysis: Same but with adjustment for adherence via inverse probability weighting with baseline covariates age, sex, mode of HIV acquisition, ethnicity, cohort, history of abacavir use and time-varying covariates time on ART, CD4 count, history of AIDS, HCV/HBV co-infection, BMI, cholesterol, hypertension, smoking and diabetes, chronic kidney disease	Same with sequential target trial emulation.

ART=antiretroviral therapy; BMI=body mass index; HCV=hepatitis C virus; HBV=hepatitis B virus; INSTI=integrase strand-transfer inhibitor

Appendix II. Participating cohorts and number of persons contributing to sequential trials from each cohort in the analyses

The following cohorts contributed to the analysis: Athens Multicenter AIDS Cohort Study (AMACS; Greece); the ANRS CO3 Aquitaine Cohort (Aquitaine; France); Stichting HIV Monitoring / AIDS Therapy Evaluation in the Netherlands study (ATHENA; Netherlands); Boston Medical Center (BMC; USA) cohort; Canadian Co-Infection Cohort (CCC; Canada); Spanish *HIV* Research Network (*CoRIS; Spain*) cohort; Italian Cohort of Antiretroviral-Naïve Patients (ICONA; Italy); Primary Infection cohort (PRIMO; France) and seroconverters and primary infection cohort (SEROPRI; France); South Alberta Clinic (SAC; Canada) cohort; Swiss HIV Cohort Study (SHCS; Switzerland); Veterans Aging Cohort Study (VACS; USA). The number of person-trials from each cohort included in the analysis are shown in the table below.

Table. Persons contributing to sequential trials from each eligible cohort included in the analyses in ART-naïve and ART-experienced individuals

	ART-naïve		**ART-experienced**	
Cohort (%)	**Initiators of INSTI – 10,767 person-trials**	**Non-Initiators of INSTI – 8,292 person-trials**	**Initiators of INSTI – 7,875 person trials**	**Non-initiators of INSTI – 373,965 person trials**
AMACS	387 (3.6%)	563 (6.8%)	117 (1.5%)	16,515 (4.4%)
Aquitaine	88 (0.8%)	93 (1.1%)	437 (5.5%)	16,546 (4.4%)
Athena	1,405 (13%)	1,926 (23%)	954 (12%)	80,271 (22%)
BMC	239 (2.2%)	119 (1.4%)	86 (1.1%)	1,694 (0.5%)
CCC	9 (0.08%)	16 (0.19%)	40 (0.5%)	3,851 (1.0%)
Coris	3,236 (30%)	1,763 (21%)	640 (8.1%)	37,344 (10%)
Icona	2,873 (27%)	1,946 (23%)	421 (5.3%)	41,520 (11%)
Primo	378 (3.5%)	432 (5.2%)	133 (1.7%)	5,100 (1.4%)
SAC	98 (0.91%)	131 (1.6%)	122 (1.5%)	7,420 (2.0%)
Seropri	-	-	2 (0.03%)	205 (0.05%)
SHCS	594 (5.5%)	424 (5.1%)	1,500 (19%)	58,723 (16%)
VACS	1,460 (14%)	879 (11%)	3,423 (43%)	104,776 (28%)

Appendix III. Definition and coding of cardiovascular events across cohort

Cohort	**Definition and coding of cardiovascular events**
AMACS	Clinical diagnostic codes for myocardial infarction, stroke and invasive cardiovascular procedure based on HIV Cohorts Data Exchange Protocol (HICDEP) coding[1]; Cause of death related to myocardial infarction or stroke based on HICDEP and Coding of Death (CoDe) coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
Aquitaine	Clinical diagnostic codes for myocardial infarction, stroke and invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
Athena	Clinical diagnostic codes for myocardial infarction, stroke and invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding
BMC	ICD-9 and ICD-10 codes for stroke and myocardial infarction: Stroke: ICD-9 codes '430'-'438' or ICD-10 codes 'I.60'-'I.63', 'I.67.8', 'I.67.9'; Myocardial infarction: ICD-9 codes '410', '412' or ICD-10 code 'I.21'; No inclusion of invasive cardiovascular procedures; No information on cause of death
CCC	Cardiovascular events recorded as a single event category without distinction between different events; Cause of death related to cardiovascular disease without distinction between cardiovascular events

Cohort	Definition and coding of cardiovascular events
CoRIS	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding
Icona	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding
Primo	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
SAC	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
Seropri	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
SHCS	Clinical diagnostic codes for myocardial infarction, stroke or invasive cardiovascular procedure based on HICDEP; Cause of death related to myocardial infarction or stroke based on HICDEP and CoDe coding or ICD-10 codes 'I.21' or 'I.60'-'I.63', 'I.67.8', 'I.67.9'
VACS	ICD-9 and ICD-10 codes for stroke and myocardial infarction: Stroke: ICD-9 codes '430'-'438' or ICD-10 codes 'I.60'-'I.63', 'I.67.8', 'I.67.9'; Myocardial infarction: ICD-9 codes '410', '412' or ICD-10 code 'I.21'; No inclusion of invasive cardiovascular procedures; No information on cause of death

Appendix IV. Process of validation of cardiovascular events and cause of death by cohort

Cohort	Event validation process
AMACS	Event information based on formal medical reports and hospitalization records; no routine validation performed
Aquitaine	For a subset of patients events were validated until 2018; there has been no validation of events occurring later. All events linked to death are validated by the clinician before coding
Athena	Standard routine validation performed by a medical doctor for all clinical events; validation of myocardial infarctions using electrocardiogram data, reported symptoms, procedures and enzyme levels; validation of strokes using reported symptoms, procedures and imaging data; validation of invasive cardiovascular procedure using information on performed procedures; cause of death information based on admission letter for admission related to death, discharge letter or autopsy report. Causal relation between conditions leading to death must be: a condition that directly caused death; due to or as a consequence of; condition that initiated the train of morbid events
BMC	No routine validation performed
CCC	Collection of information from medical records at each cohort visit without standardized event validation
CoRIS	No routine validation performed
Icona	Routine validation of events for a subset of cohort participants only (about 25%); for this subset, validation of myocardial infarctions is performed using electrocardiogram data, reported symptoms, procedures and enzyme levels; validation of strokes using reported symptoms, procedures and imaging data; validation of invasive cardiovascular procedure using information on performed procedures; cause of death information based on admission letter for admission related to death, discharge letter or autopsy report. Causal relation between conditions leading to death must be: a condition that directly caused death; due to or as a consequence of; condition that initiated the train of morbid events
Primo	Reported by the treating physician; no routine validation performed
SAC	Reported by patient care provider site; no routine validation performed
Seropri	Reported by the treating physician; no routine validation performed

Cohort	Event validation process
SHCS	Events collected according to a standardized definition and registered using a dedicated case report form and validated from a senior HIV physician at the cohort site; validation of myocardial infarctions using electrocardiogram data, reported symptoms, procedures and enzyme levels; validation of strokes using reported symptoms, procedures and imaging data; validation of invasive cardiovascular procedure using information on performed procedures; cause of death information based on admission letter for admission related to death, discharge letter or autopsy report. Causal relation between conditions leading to death must be: a condition that directly caused death; due to or as a consequence of; condition that initiated the train of morbid events
VACS	Event information is based on ICD-9/ICD-10 codes (high agreements of codes with formal chart adjudication has been demonstrated) [2,3,4]

Appendix V. Definition of implausible values for covariates

Implausible values set to missing based on the following definitions:

Height, weight and BMI: height <1.0 meter; weight ≥295 kilograms/650 lbs; BMI <12 or ≥100[5];
Total cholesterol: <1.75mmol/L or >20mmol/L or <67.67 and >773.4 mg/dL[6,7];
Blood pressure: systolic blood pressure <70 or ≥270 mmHg; diastolic blood pressure <50 or ≥150 mmHg[8]);
Creatinine to define eGFR and chronic kidney disease: ≤0.01 or >30

Appendix VI. Five most frequently used INSTI-based and non-INSTI-based ART regimens at trial baseline (in descending order)

ART-naïve		**ART-experienced**	
Initiators of INSTI	**Non-initiators of INSTI**	**Initiators of INSTI**	**Non-initiators of INSTI**
Lamivudine (3TC) + Abacavir (ABC) + Dolutegravir (DTG) (n=2,120; 20%)	Darunavir (DRV) + Ritonavir (RTV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=1,800 24%)	Lamivudine (3TC) + Abacavir (ABC) + Dolutegravir (DTG) (n=2,277; 29%)	Efavirenz (EFV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=97,209; 26%)
Emtricitabine (FTC) + Tenofovir Alafenamide Fumarate (TAF) + Bictegravir (BIC) (n=1,943; 18%)	Rilpivirine (RPV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=1,327; 18%)	Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) + Elvitegravir (EVG) (n=1,063; 13%)	Rilpivirine (RPV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=44,626; 12%)
Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) + Dolutegravir (DTG) (n=1,599; 15%)	Efavirenz (EFV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=1,080; 15%)	Emtricitabine (FTC) + Tenofovir Alafenamide Fumarate (TAF) + Elvitegravir (EVG) (n=767; 10%)	Darunavir (DRV) + Ritonavir (RTV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=36,775; 10%)
Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) + Elvitegravir (EVG) (n=1,418; 13%)	Darunavir (DRV) + Emtricitabine (FTC) + Tenofovir Alafenamide Fumarate (TAF) (n=517; 7.0%)	Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) + Dolutegravir (DTG) (n=484; 6.1%)	Atazanavir (ATV) + Ritonavir (RTV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=29,577; 7.9%)

ART-naïve		**ART-experienced**	
Initiators of INSTI	**Non-initiators of INSTI**	**Initiators of INSTI**	**Non-initiators of INSTI**
Emtricitabine (FTC) + Tenofovir Alafenamide Fumarate (TAF) + Elvitegravir (EVG) (n=1,264; 12%)	Atazanavir (ATV) + Ritonavir (RTV) + Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) (n=428; 5.8%)	Emtricitabine (FTC) + Tenofovir Disoproxil Fumarate (TDF) + Raltegravir (RLT) (n=295; 3.7%)	Nevirapine (NVP) + Lamivudine (3TC) + Abacavir (ABC) (n=19,820; 5.3%)
TOTAL (n=8,344; 77%)	**TOTAL (n=5,152; 62%)**	**TOTAL (n=4,886; 62%)**	**TOTAL (n=228,007; 61%)**

Appendix VII. Results of sensitivity analyses in ART-naïve and ART-experienced individuals

	4-year risk in ART-naïve individuals (95% CI)				4-year risk in ART-experienced individuals (95% CI)			
Model	**Initiators of INSTI**	**Non-initiators of INSTI**	**Risk ratio**	**Risk difference**	**Initiators of INSTI**	**Non-initiators of INSTI**	**Risk ratio**	**Risk difference**
Relaxed definition of eligibility*	0.70% (0.53, 0.88)	0.80% (0.64, 0.97)	0.88 (0.62, 1.23)	-0.093% (-0.35, 0.15)	1.58% (1.31, 1.68)	1.42% (1.31, 1.50)	1.11 (0.94, 1.20)	0.15% (-0.090, 0.27)
Restricting Initiators to top three most used INSTI regimens**	0.65% (0.26, 1.29)	0.81% (0.58, 1.08)	0.81 (0.30, 1.73)	-0.16% (-0.70, 0.53)	1.46% (0.74, 2.83)	1.48% (1.28, 1.71)	0.99 (0.48, 1.93)	-0.021% (-0.79, 1.39)
Restricting ART-naïve Initiators to dolutegravir- or bictegravir-based regimens	0.88% (0.41, 1.39)	0.80% (0.59, 1.06)	1.10 (0.45, 1.98)	0.080% (-0.4, 0.37)	NA	NA	NA	NA
Only including cohorts with information on all types of CVD events+	0.75% (0.46, 1.05)	0.75% (0.51, 1.04)	1.00 (0.57, 1.64)	-0.0086% (-0.24, 0.19)	1.67% (0.98, 2.54)	1.93% (1.58, 2.28)	0.87 (0.51, 1.35)	-0.26% (-0.96, 0.60)
Excluding SHCS from analysis in ART-naïve individuals	0.71% (0.49, 0.96)	0.77% (0.54, 1.04)	0.92 (0.54, 1.50)	-0.060% (-0.43, 0.30)	NA	NA	NA	NA
Excluding Athena, Icona and SHCS from analyses because these cohorts were included in the prior study by RESPOND	0.54% (0.30, 0.84)	0.48% (0.25, 0.76)	1.13 (0.50, 2.60)	0.061% (-0.32, 0.46)	0.95% (0.60, 1.54)	0.93% (0.78, 1.11)	1.02 (0.65, 1.58)	0.022 (-0.37, 0.58)
Additionally adjusting for cumulative months on PIs and NRTI that have been associated with CVD in previous studies ++	NA	NA	NA	NA	1.41% (0.88, 2.01)	1.48% (1.28, 1.71)	0.95 (0.60, 1.35)	-0.070% (-0.61, 0.51)
Additionally adjusting for current use of TAF that has been associated with weight gain in previous studies	0.76% (0.51, 1.04)	0.75% (0.53, 1.01)	1.03 (0.56, 1.70)	0.019% (-0.42, 0.43)	1.41% (0.88, 2.00)	1.48% (1.29, 1.71)	0.95 (0.60, 1.35)	-0.068% (-0.60, 0.52)
Additionally adjusting for CD4 count nadir+++	0.77% (0.52, 1.07)	0.75% (0.53, 1.01)	1.02 (0.62, 1.68)	0.018% (-0.37, 0.41)	1.41% (0.94, 2.10)	1.48% (1.29, 1.72)	0.95 (0.64, 1.42)	-0.068% (-0.56, 0.58)
Restrict follow-up to years from 2016 onwards	0.82% (0.50, 1.24)	0.73% (0.34, 1.31)	1.11 (0.51, 2.52)	0.081% (-0.58, 0.62)	0.86% (0.17, 2.71)	1.02% (0.52, 2.16)	0.84 (0.19, 2.46)	-0.16% (-1.18. 1.31)
Restrict the analysis to men	0.79% (0.53, 1.11)	0.73% (0.49, 1.01)	1.08 (0.62, 1.74)	0.061% (-0.35, 0.45)	1.65% (1.09, 2.48)	1.57% (1.36, 1.81)	1.05 (0.70, 1.56)	0.083% (-0.49, 0.87)

*HIV-RNA measurement not required in the current month but CD4 and HIV-RNA measurement only required in last 3 months; **in ART-naïve individuals this includes: 3TC+ABC+DTG; FTC+TAF+BIC; FTC+TDF+DTG; In ART-experienced individuals: 3TC+ABC+DTG; FTC+TDF+EVG; FTC+TAF+EVG; +cohorts included: AMACS, Aquitaine, Athena, Coris, Icona, Primo, SAC, Seropri, SHCS; 95% confidence intervals obtained from bootstrapping with 200 samples; ++protease inhibitors indinavir, ritonavir-boosted lopinavir, darunavir and nucleoside reverse transcriptase inhibitor didanosine; +++modeled using restricted cubic splines with three knots; TAF=tenofovir alafenamide; CI=confidence interval; SHCS=Swiss HIV Cohort Study

Appendix VIII. Cardiovascular event hazard ratios for covariates from multivariable pooled logistic regression models in both ART-naïve and ART-experienced populations

Covariates	Hazard ratio in ART-naïve individuals (95% CI)+	Hazard ratio in ART-experienced individuals (95% CI)+
Sex		
Male	1.0	1.0
Female	0.67 (0.31, 1.13)	0.47 (0.34, 0.64)
Age**		
Coefficient 1	1.15 (1.10, 1.21)	1.10 (1.08, 1.14)
Coefficient 2	0.93 (0.89, 0.97)	0.97 (0.95, 0.99)
Time since first started ART**	-	
Coefficient 1		1.01 (0.98, 1.04)
Coefficient 2		1.00 (0.97, 1.02)
Ethnicity		
White	1.0	1.0
Minority ethnicity	1.0 (0.34, 2.15)	1.15 (0.85, 1.55)
Unknown	0.50 (0.10, 2.75)	1.37 (0.70, 2.37)
Mode of HIV acquisition		
Sex between men	1.0	1.0
Heterosexual contact	1.24 (0.72, 2.15)	1.18 (0.93, 1.49)
Injection drug use	1.26 (0.00087, 4.31)	1.29 (0.85, 1.94)
Other/unknown	1.84 (0.78, 3.65)	1.18 (0.79, 1.68)
AIDS diagnosis		
No	1.0	1.0
Yes	1.51 (0.78, 2.99)	1.05 (0.84, 1.29)
Natural log of CD4 count (in cells/ µl **		
Coefficient 1	0.87 (0.71, 1.11)	0.76 (0.62, 1.00)
Coefficient 2	0.95 (0.71, 1.11)	1.28 (0.98, 1.57)
Natural log of HIV RNA (in copies/ml) **		-
Coefficient 1	3.77 (1.07, 7611.93)	
Coefficient 2	0.02 (0.00, 0.98)	
Hepatitis C co-infection		
No	1.0	1.0
Yes	0.73 (0.15, 1.65)	1.09 (0.84, 1.38)
Hepatitis B co-infection		
No	1.0	1.0
Yes	0.63 (0.0014, 1.85)	0.85 (0.52, 1.21)
BMI >25		
No	1.0	1.0
Yes	0.71 (0.33, 1.23)	1.03 (0.85, 1.23)
Missing	1.04 (0.58, 1.82)	1.15 (0.76, 1.68)
High total cholesterol (≥240 mg/dL / >6.18 mmol/L)		
No	1.0	1.0
Yes	3.73 (1.35, 7.72)	1.33 (1.10, 1.60)
Missing	1.60 (0.96, 2.74)	1.01 (0.59, 1.58)
Uncontrolled hypertension (systolic ≥130 or diastolic ≥80 mmHg)		
No	1.0	1.0
Yes	1.13 (0.67, 1.92)	1.34 (1.16, 1.58)
Missing	1.14 (0.58, 2.22)	0.98 (0.65, 1.47)
Smoking		
Never smoker	1.0	1.0
Current smoker	1.95 (1.02, 4.16)	1.95 (1.57, 2.44)
Ex-smoker	2.42 (1.08, 5.87)	1.49 (1.16, 2.01)
Missing	1.20 (0.60, 2.44)	0.97 (0.71, 1.39)
Diabetes Mellitus		
No	1.0	1.0
Yes	1.66 (0.73, 3.23)	1.63 (1.27, 2.04)
Chronic kidney disease ≥stage 3 (eGFR<60)		
No	1.0	1.0
Yes	3.77 (0.72, 9.47)	1.38 (0.96, 1.89)
Missing	0.52 (0.096, 1.22)	0.53 (0.25, 1.21)

Covariates	Hazard ratio in ART-naïve individuals (95% CI)+	Hazard ratio in ART-experienced individuals (95% CI)+
Abacavir use (at baseline in ART-naïve and within 6 months previously in ART-experienced)		
No	1.0	1.0
Yes	0.44 (0.12, 0.88)	1.45 (1.19, 1.78)

**modeled as restricted cubic splines with three knots; +95% confidence intervals from bootstrapping with 500 samples

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