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Antiretroviral Therapy and Cardiovascular Risk in People With HIV in the United States—An Updated Analysis

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Background. Several antiretroviral therapy (ART) medications have been associated with increased cardiovascular risk, but less is known about the safety of modern ART. We sought to compare the risk of major adverse cardiac events (MACEs) among different ART regimens.

Methods. Using insurance claims databases from 2008 to 2020, we identified adults aged <65 years who newly initiated ART. We compared non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens to protease inhibitors (PI)- and integrase inhibitors (INSTI)-based regimens. We used propensity score-weighted Kaplan-Meier functions to estimate the 6, 12, 18, 24, 36, and 48 months' risk and risk differences (RD) of MACE.

Results. Among 37 935 ART initiators (median age, 40 years; 23% female; 26% Medicaid-insured), 45% started INSTI-, 16% PI-, and 39% NNRTI-based regimens. MACE occurred in 418 individuals (1.1%) within 48 months after ART initiation. Compared to NNRTI initiators, the risk of MACE was higher at 12 months (RD, 0.50; 95% CI, 0.14–0.99), 18 months (RD, 0.53; 95% CI, 0.11–1.06), and 24 months (RD, 0.62; 95% CI, 0.04–1.29) for PI initiators, and at 12 (RD, 0.20; 95% CI, 0.03–0.37) and 18 months (RD, 0.31; 95% CI, 0.06–0.54) for INSTI initiators; the precision of estimates was limited for longer duration of follow-up.

Conclusions. Among ART initiators, PI-based and INSTI-based regimens were associated with higher short-term risk of MACE compared to NNRTI-based regimens. The pattern of association between INSTIs and PIs with excess risk of MACE was similar.

Keywords. antiretroviral therapy; cardiovascular disease; HIV; integrase strand transfer inhibitors; protease inhibitors.

People with HIV in the United States who receive successful treatment are now dealing with the burden of coexisting age-associated conditions [1–3]. Moreover, people with HIV have higher prevalence of comorbidities than people without HIV, and these can occur at earlier ages [4, 5].

During the past 2 decades, multiple studies have reported associations between antiretroviral therapy (ART) and cardiovascular disease (CVD) risk [6–9]. In our prior study using data from 2008 to 2015, we reported that integrase strand-transfer inhibitor (INSTI) initiation was associated with decreased risk of incident CVD compared to initiation non-INSTI regimens [10]. However, accumulating evidence shows that INSTIs, particularly second-generation INSTIs, are associated with abnormal weight gain, hypertension, and metabolic complications [11–15], which are risk factors for CVD. Since 2017, INSTI-based regimens have become the only preferred ART regimens per the US Department of Health and Human Services guidelines [16]. Conversely, prior research has shown that protease inhibitors (PIs), but not nonnucleoside reverse transcriptase inhibitors (NNRTI), are associated with increased CVD risk [8].

In this study, we sought to perform an updated analysis of the relationship between different ART regimens and risk of major adverse cardiac events (MACEs) in a cohort of adult ART initiators with HIV in the United States.

METHODS

Data Source

We used data from the Merative MarketScan Commercial (2008–2020) and Multi-state Medicaid (2011–2020) databases. Individual-level information on health insurance enrollment, inpatient and outpatient diagnoses and procedures, and outpatient pharmacy-dispensed medications are contained within these databases for commercially insured persons from

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participating employers and health plans and individuals covered by Medicaid from US states submitting data. The institutional review board at Washington University in St. Louis School of Medicine deemed this study exempt from human subject review.

Study Design and Population

We identified adults with HIV who initiated ART from 1 January 2008 through 30 June 2020. ART initiators were defined as persons with at least 6 months of continuous healthcare enrollment (ie, baseline period) before initiation of stable ART. Stable ART was defined as previously reported [10]. In brief (1) consistently being in possession of an ART regimen without having a period of ≥60 days in which a component of the regimen was missing and (2) a medication possession ratio (the percentage of time a person had access to medications) ≥80% for at least 180 days [17]. An ART regimen was defined as a combination of drugs that contained (1) 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 drug from a different class such as INSTI, PI, NNRTI, entry inhibitor, or fusion inhibitor; (2) any 3-drug combination from different classes (NRTI, NNRTI, PI, INSTI, entry inhibitors, or fusion inhibitors); (3) INSTI (dolutegravir) plus NNRTI (rilpivirine) or NRTI (lamivudine); or (4) PI plus INSTI or NNRTI. PI-based regimens were restricted to combinations that included a booster. We defined an ART regimen switch, and thus the termination of a stable regimen, as the addition or removal of a class of ART. In-class substitutions were not considered a new regimen. We excluded persons with a history of MACE before the start of the first stable regimen, using an all-available lookback period [18].

Outcomes and Covariates

We defined outcomes and covariates using International Classification of Diseases (ICD), Ninth Revision, Clinical Modification, and ICD-10, Clinical Modification, diagnosis and procedure codes and Current Procedural Terminology, 4th edition, codes (Supplementary Tables 1 and 2). The outcome, MACE, was a composite of myocardial infarction, ischemic stroke, coronary artery bypass grafting, and percutaneous coronary intervention [10].

Baseline covariates including age, sex, Medicaid insurance status, CVD medications, and comorbidities, including standard definitions using the Elixhauser algorithm [19] were identified using an all-available lookback period [18] before initiation of a stable ART regimen. All the included covariates are outlined in Supplementary Table 3.

Statistical Analysis

We summarized baseline characteristics by treatment group using descriptive statistics. We used 2 treatment group classifications based on the composition of each individual's initial ART regimen: (1) 3-level analysis: INSTI-based, PI-based, or NNRTI-based; and (2) 6-level analysis: raltegravir (RAL)-based, elvitegravir (EVG)-based, dolutegravir (DTG)-based, bictegravir (BIC)-based, PI-based, and NNRTI-based. We categorized treatment this way for 2 reasons: first, evidence suggests that the risk of CVD varies by ART (among classes and individual drugs); second, INSTI-based regimens are the most common contemporary ART regimen.

We fit separate propensity score models using multinomial logistic regression models for the 3- and 6-level treatment definitions. A complete list of variables included in the models are shown in Supplementary Tables 4a and 4b. Stabilized inverse probability treatment weights were calculated from propensity scores as the proportion of sample receiving a given treatment/estimated probability of receiving that treatment, based on the predicted values obtained from the multinomial logistic regression models [20]. Trimming based on the distribution of the propensity scores was applied to achieve balance in all measured covariates [21]. An absolute standardized mean difference <0.1 was considered to indicate adequate balance of observed covariates after weighting the population [22].

We then estimated the weighted cumulative risk of MACE, defined as 1 – the Kaplan-Meier survival estimator, using adjusted Kaplan-Meier methods that allow for estimation of treatment effects over the course of follow-up [23]. The first 90 days of follow-up were excluded to allow for time between exposure and development of diseases (induction period) to reduce the potential for spurious associations. Individuals were followed from the date of stable ART regimen until the first occurrence of any MACE outcome or a censoring event. A censoring event was considered the earliest of 90 days post-ART regimen switch, health plan disenrollment, or end-of-study on 31 December 2020. Censoring did not occur immediately at regimen switch but rather 90 days later because events in this timeframe could potentially be related to the index ART regimen. We calculated cumulative risk differences (RD) between treatment groups and computed 95% confidence intervals (CI) using a nonparametric bootstrap with 250 samples.

RESULTS

We identified 37 935 eligible ART initiators, including 27 962 (74%) commercially insured and 9973 (26%) Medicaid-insured adults. The distribution of ART regimens initiated was as follows: INSTI-based (45%), PI-based (16%), and NNRTI-based (39%). Among INSTI initiators, 14% started RAL, 40% EVG, 30% DTG, and 16% BIC. Most PI initiators started atazanavir (43%) or darunavir (38%), whereas most NNRTI initiators started efavirenz (78%) or rilpivirine (18%). Abacavir (ABC) was used in 13% of all regimens (21% of INSTI-, 14% of PI-, and 3% of NNRTI-based regimens). Tenofovir disoproxil fumarate (TDF) was included in 51% of INSTI-, 96% of PI-, and 99% of NNRTI-based regimens, whereas tenofovir

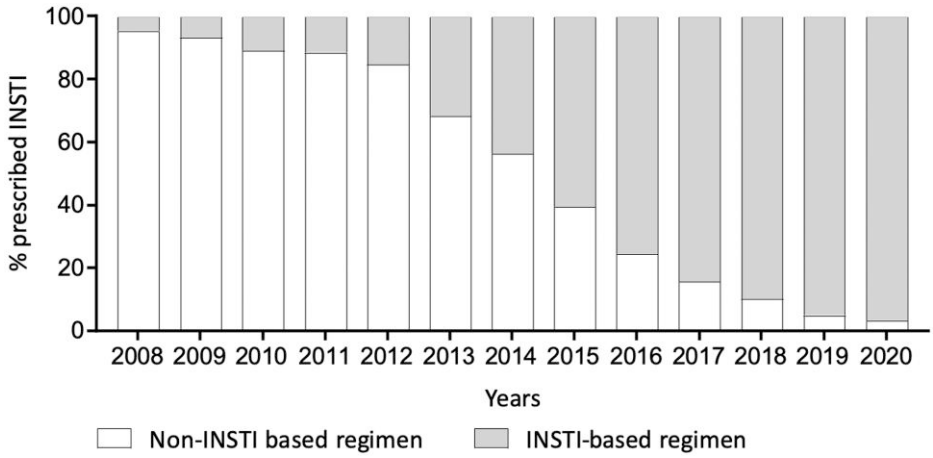

Figure 1. Proportion of new ART users initiated on INSTI for 2008 to 2020. Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand-transfer inhibitor.

alafenamide (TAF) was included in 48% of INSTI, 4% of PI-, and <1% of NNRTI-based regimens. The annual proportion of INSTI-based ART initiation increased dramatically from 2008 (5%) to 2020 (97%) (Figure 1).

In the overall study population, the median (interquartile range) age was 40 (30, 49) years, 23% were female, 15% had a diagnosis of hypertension, 6% diabetes, and 2% hepatitis C. Lipid-lowering drugs were prescribed in 14% of participants and 10% had documented tobacco use. Table 1 and Supplementary Table 5 present participants characteristics by ART regimen. After propensity score weighting, the distribution of covariates was well-balanced among treatment groups (all standardized mean differences <0.1) (Supplementary Table 4*A* and 4*B*).

The median (interquartile range) follow-up duration for those starting INSTI-, PI-, and NNRTI-based regimens was 442 (224, 894), 429 (212, 932), and 521 (239, 1109) days, respectively. Over the study period, the MACE outcome occurred in 418 individuals (1.1%) (INSTI, n = 199 [1.2%]; PI, n = 87 [1.4%]; NNRTI, n = 132 [0.9%]). The number of individual and composite MACE outcome events, censoring events, and person-time at risk are presented in Supplementary Tables 6*A* and 6*B*.

Figure 2 illustrates the weighted risks and risk differences of MACE in the 3-level analysis. The weighted risks at all specified time points (6, 12, 18, 24, 36, and 48 months) (Table 2) were highest for PI-based regimens and lowest for NNRTI-based regimens, with the widest gap in risk during the first 24 months. The weighted risks of MACE diverged early on (6-month weighted risks [95% CI]: INSTI, 0.28 [0.21–0.39]; PI, 0.50 [0.32–0.76]; NNRTI, 0.19 [0.12–0.29]) and persisted over the follow-up period (48-month weighted risks [95% CI]: INSTI, 2.32 [1.90–2.82]; PI, 2.69 [1.94–3.73]; NNRTI, 1.78 [1.43–2.22]). Compared to NNRTI-based ART initiators, the risk was significantly higher for PI initiators at 12 months (RD, 0.50; 95% CI [0.14–0.99]), 18 months (RD, 0.53; 95% CI [0.11–1.06]), and 24 months (RD, 0.62; 95% CI [0.04–1.29]); these risks correspond to 5, 5, and 6 more events per 1000 patients, respectively (Table 2). Compared to NNRTI-based ART initiators, the risk was also significantly higher for INSTI-based ART at 12 months (RD, 0.20; 95% CI [0.03–0.37]) and 18 months (RD, 0.31; 95% CI, 0.06–0.54]); these risks correspond to 2 and 3 more events per 1000 patients, respectively (Table 2). We did not observe differences in risk between PI-based versus INSTI-based ART initiators, although this could be related to the smaller size of those groups (Supplementary Table 7).

Figure 3 illustrates the estimated cumulative risks and risk differences of MACE in the 6-level analysis. We did not observe differences in risk at any of the specified periods between NNRTI-based ART and individual INSTI drugs, as indicated

Table 1. Selected Baseline Characteristics of Participants by Initial ART

Characteristic	NNRTI-based Regimens n = 14 692 (%)	PI-based Regimens n = 6136 (%)	INSTI-based Regimens n = 17 107 (%)
Age, y (median, IQR)	41 (32, 49)	42 (33, 49)	38 (28, 49)
Male	11 852 (80.7)	4144 (67.5)	13 347 (78.0)
Medicaid insured	2419 (16.5)	1962 (32.0)	5592 (32.7)
Hypertension	2034 (13.8)	916 (14.9)	2980 (17.4)
Diabetes	783 (5.3)	373 (6.1)	1194 (7.0)
Obesity	705 (4.8)	376 (6.1)	1954 (11.4)
Chronic kidney disease	94 (0.6)	109 (1.8)	279 (1.6)
Tobacco use	570 (3.9)	329 (5.4)	2738 (16.0)
Lipid-lowering therapy	1740 (11.8)	703 (11.5)	2758 (16.1)
Drug use	750 (5.1)	605 (9.9)	1944 (11.4)
Hepatitis B infection	23 (0.2)	21 (0.3)	280 (1.6)
Hepatitis C infection	65 (0.4)	44 (0.7)	576 (3.4)
Depression	826 (5.6)	488 (8.0)	1965 (11.5)

Abbreviations: ART, antiretroviral therapy; INSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

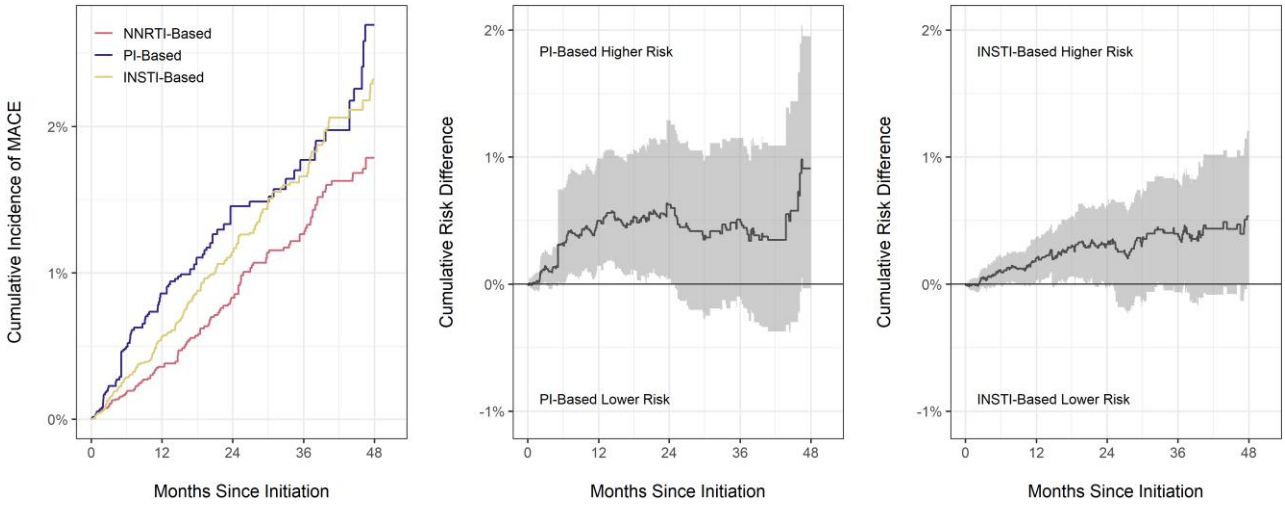

Figure 2. Propensity score-weighted cumulative risk and risk difference estimates of MACE by major ART classes. NNRTI served as the reference group. Abbreviations: ART, antiretroviral therapy; MACE, major adverse cardiac event; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand-transfer inhibitor.

by 95% CIs that included the null; however, there was a tendency for increased risk with all INSTI drugs, except for RAL (Figure 3 and Supplementary Table 8).

Secondary analyses were performed to account for TDF, TAF, or ABC use (Supplementary Tables 9–11). Among INSTI-based ART initiators, there were no differences in risk in those using TAF- or ABC-containing combinations as compared to TDF-containing combinations. Among PI initiators, those using a TAF-containing combination had lower risk at 6 months (RD, −0.13; 95% CI [−0.25, −0.03]) and 12 months (RD, −0.46; 95% CI [−0.73, −0.27]) compared to TDF-containing combinations, but not in later time points. Among PI initiators, ABC use was not associated with changes in risk of MACE compared to TDF. Last, among NNRTI-based ART initiators, there was no difference in the risk of MACE between those using regimens containing ABC as compared to TDF.

DISCUSSION

In this active comparator, new-user study among people with HIV in the United States, we observed higher short-term risk of MACE among initiators of PI- or INSTI-based ART regimens compared to NNRTI-based regimens, after accounting for differences in baseline demographic and clinical characteristics. The risk of MACE was higher at 12, 18, and 24 months for PI initiators, and at 12 and 18 months for INSTI initiators, compared to NNRTI-based ART initiators. The highest difference in risk for those on INSTI-based ART was observed at 18 months, whereas for PI initiators it was at 24 months. We did not observe a difference in risk of MACE between INSTI versus PI initiators.

Our team previously reported a 21% decreased risk of MACE associated with INSTI-based ART initiation compared to non–INSTI-based ART initiation, in a study with median follow-up of approximately 18 months [10]. In this updated analysis, we used a different approach. Given the potentially different risk profile of PI-based regimens compared to NNRTI-based regimens, we compared the effects of ART initiation with each of the 3 main anchor drugs–based regimens (PI-based vs INSTI-based vs NNRTI-based regimens) on the risk of MACE, which allows a more detailed risk assessment. In addition, in the prior analysis that included data from 2008 to 2015, most participants in the INSTI group initiated first-generation INSTIs such as RAL (33%) and EVG (49%), with only 19% initiating DTG and no initiators of BIC. However, second-generation INSTIs (DTG and BIC) have become the preferred drugs in first-line HIV treatment worldwide in recent years [16, 24]. In fact, in the current analysis, we found a pronounced increase in the proportion of people initiating INSTI-based ART over time, from 5% in 2008 to 97% in 2020, and a greater proportion of participants initiated second-generation INSTI (30% DTG and 16% BIC). Additionally, given the lack of a well-established comparator group in recent years, this updated analysis used weighted cumulative incidence functions to study individual treatment groups, considering INSTI, PI, and NNRTI initiators separately. This approach allows for better estimates of the risk of MACE in each treatment group while accounting for the presence of confounders.

Compared to the NNRTI group, PI-based and INSTI-based ART initiators had diverging weighted risk of MACE early after ART initiation. Increased risk of CVD in people using some PIs, including indinavir, ritonavir-lopinavir, and ritonavir-

Table 2. Weighted Cumulative Risk and Risk Difference Estimates of Incident MACE

Regimen Type	6 mo		12 mo		18 mo		24 mo		36 mo		48 mo	
	Cumulative Risk (95% CI)	Risk Difference (95% CI)	Cumulative Risk (95% CI)	Risk Difference (95% CI)	Cumulative Risk (95% CI)	Risk Difference (95% CI)	Cumulative Risk (95% CI)	Risk Difference (95% CI)	Cumulative Risk (95% CI)	Risk Difference (95% CI)	Cumulative Risk (95% CI)	Risk Difference (95% CI)
NNRTI	0.19 (0.12–0.29)	Reference	0.36 (0.26–0.50)	Reference	0.57 (0.43–0.76)	Reference	0.83 (0.64–1.08)	Reference	1.26 (1.00–1.59)	Reference	1.78 (1.43–2.22)	Reference
PI	0.50 (0.32–0.76)	0.31 (−0.01 to 0.75)	0.86 (0.61–1.21)	0.50 (0.14–0.99)	1.10 (0.80–1.53)	0.53 (0.11–1.06)	1.45 (1.06–1.99)	0.62 (0.04–1.29)	1.77 (1.29–2.42)	0.51 (−0.10–1.15)	2.69 (1.94–3.73)	0.91 (−0.03–1.95)
INSTI	0.28 (0.21–0.39)	0.10 (−0.01 to 0.22)	0.56 (0.44–0.72)	0.20 (0.03–0.37)	0.88 (0.71–1.08)	0.31 (0.06–0.54)	1.14 (0.94–1.40)	0.31 (−0.02 to 0.62)	1.66 (1.37–2.01)	0.39 (−0.06–0.82)	2.32 (1.90–2.82)	0.53 (−0.01–1.20)

Abbreviations: INSTI, integrase inhibitor; MACE, major adverse cardiac event; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

darunavir has been previously described [8, 9]. It is believed that the biological mechanisms of increased CVD risk in those taking PI may overlap and include pro-atherogenic lipid profile disturbances with older agents of this class and other possible mechanisms such as cholesterol derivatives accumulation within macrophages and plaque disruption with darunavir [25].

The evidence on the association between INSTI and risk of CVD remains inconclusive. In a recent prospective study of a large, multinational European cohort (RESPOND), the use of INSTI was associated with nearly a doubling in the CVD incidence rate compared to no INSTI use in the first 6 months after initiation; the CVD incidence rate remained elevated up to 24 months after initiation and decreased thereafter to levels similar to those never exposed to INSTIs [26]. Our findings support an increased short-term risk of MACE associated with ART initiation with INSTI-based regimens; however, the limited follow-up time of our study does not allow for a reliable assessment at later time points. In the Swiss HIV Cohort Study using the target trial emulation framework, the authors found no difference in the risk of CVD events in people initiating ART with INSTI-based regimens compared to non–INSTI-based ART initiators [27]. The difference in results may be related to the research question, study population, and methods. The Swiss study specifically involved treatment-naïve participants and compared the risk of CVD in those initiating an INSTI-based regimen and those initiating any other ART. However, neither that study nor the RESPOND study reported results on the CVD risk of INSTI in relation to PI- or NNRTI-based regimens, which remains an important consideration given the differential risks potentially conveyed by these drug classes. A separate analysis from the RESPOND cohort demonstrated that starting or switching to an INSTI-based regimen was associated with higher risk of hypertension compared to those receiving NNRTIs [15]. When the analysis was restricted to ART-naïve participants, the incidence of hypertension was 92% higher in those receiving INSTI than in those receiving NNRTI [adjusted incidence rate ratio (aIRR), 1.92; 95% CI, 1.51–2.44]. The risk of hypertension was similar between INSTI and PI users (aIRR, 1.01; 95% CI, 0.82–1.25).

Weight gain and metabolic syndrome are potential mediators of increased CVD risk associated with INSTI use, but the evidence is inconsistent. In the ADVANCE study, participants initiating DTG-based regimens, in particular those who received TAF-containing combinations, had increased risk of diabetes and CVD compared to those initiating efavirenz-based therapy [28]. However, a recent analysis including >2500 participants from 2 AIDS Clinical Trials Group–sponsored cohorts did not find an association between weight gain in the first year following ART initiation with any regimen and subsequent risk of MACE [29], although this study did not specifically analyze exposure to INSTI and observed few incident MACE events. In the RESPOND study, no effect was

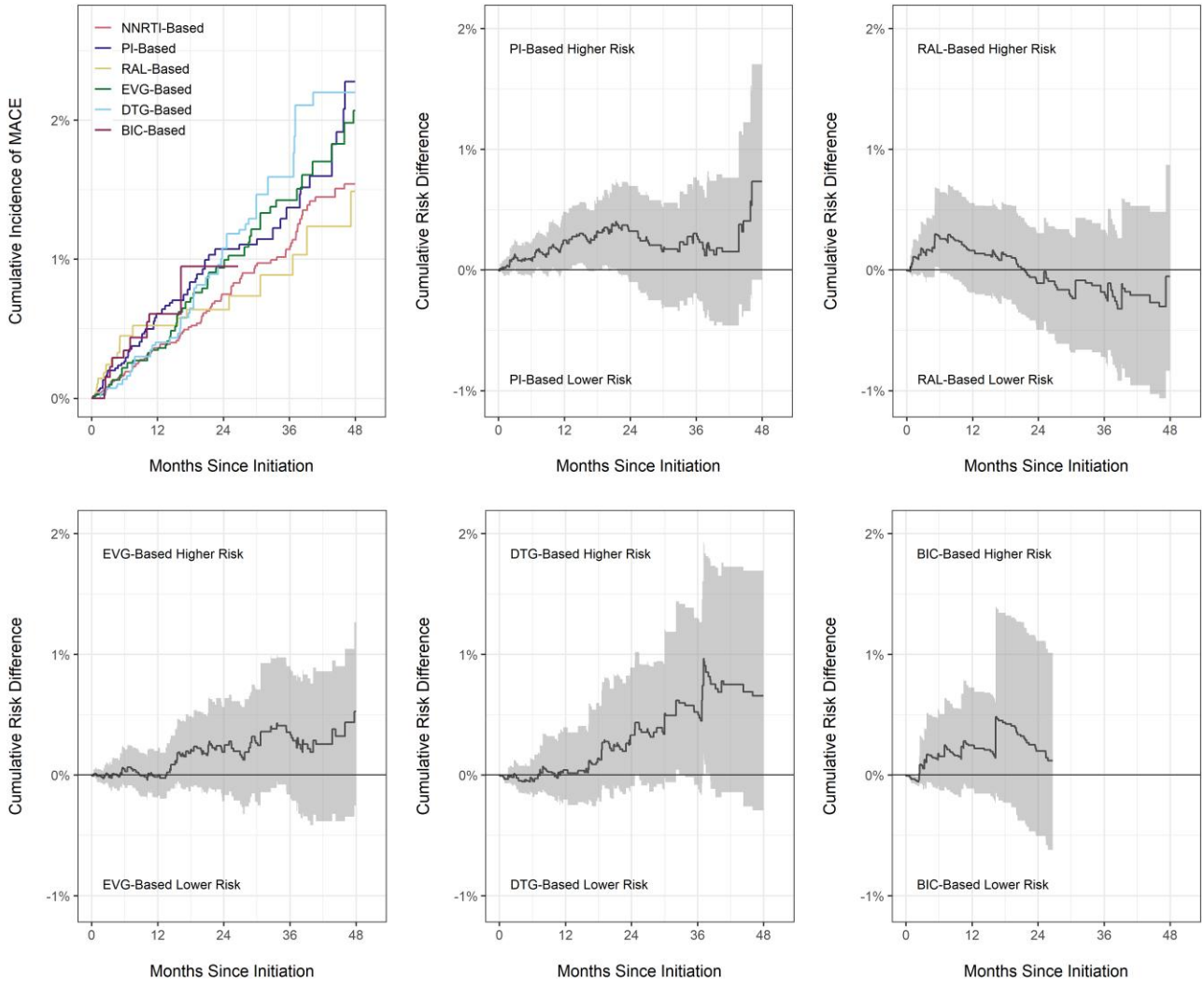

Figure 3. Propensity score-weighted cumulative risk and risk difference estimates of MACE by ART classes and individual INSTI agents. NNRTI served as the reference group. Abbreviations: ART, antiretroviral therapy; BIC, bictegravir; DTG, dolutegravir; EVG, elvitegravir; MACE, major adverse cardiac event; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

observed after accounting for time varying body mass index (BMI) and dyslipidemia in the risk of CVD in those exposed to INSTI. Although we did not include BMI in the analysis because of a lack of anthropomorphic elements in claims data, our analysis showed no difference in the risk of MACE when accounting for TAF use compared to TDF in those initiating INSTI-based ART.

Our study has several limitations. First, this was an observational analysis of administrative data, which are not collected for clinical research, and confounding by indication may persist even after accounting for a wide set of measured covariates. Second, the claims databases we used do not include race and BMI, which are relevant factors when assessing CVD risk. Although we accounted for obesity using diagnostic codes as proxy measures, this is a less reliable measurement that can be subject to undercoding. Moreover, certain important clinical characteristics such as tobacco use and family history of CVD are potentially subject to misclassification because of undercoding. Third, the precision of effect estimates decreases with increasing follow-up duration. Fourth, our eligibility criteria did not require HIV RNA tests to confirm virologic suppression, but rather just continuous prescription of the same stable ART regimen. Finally, the generalizability of our findings is likely limited only to adults younger than age 65 years covered by commercial or Medicaid health plans although the restriction to adults younger than age 65 years may explain the lower incidence of MACE we observed compared to other cohorts.

In conclusion, the results of our study among people with HIV in the United States who initiate ART suggest that PI-based or INSTI-based regimens are associated with greater short-term

risk of MACE compared to NNRTI-based regimens, and that the pattern of association between INSTIs and PIs with excess CVD risk is similar. Our large national study adds to the accumulating literature regarding ART and CVD risk and supports the need for other large, rigorous analyses exploring the role and potential mechanisms by which INSTIs may affect cardiovascular health to identify potential interventions to decrease the excess risk.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. J.O.A. conceived the study; J.S. performed the analysis; L.P.R., J.A.O., M.A.O., A.M.B., and W.G.P. interpreted the data; L.P.R. drafted the manuscript; and all authors reviewed and approved the final draft of the manuscript.

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Potential conflicts of interest. J.A.O. reports receiving investigator-initiated funds from Janssen Scientific for work unrelated to this study. M.A.O. reports consulting fees from Pfizer for work unrelated to this study. A.M.B. reports receiving investigator-initiated funds from Merck. All other authors report no potential conflicts.

Patient consent statement. This noninterventional retrospective study based on an anonymized claims database certified compliant with the Health Insurance Portability and Accountability Act was deemed exempt from full review by the institutional review board at Washington University in St. Louis School of Medicine. This study did not include factors necessitating patient consent.

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