Background: Several antiretroviral therapy (ART) classes have been associated with increased myocardial infarction (MI) risk. No studies have examined cardiovascular disease (CVD) in people living with HIV (PLWH) on integrase strand transfer inhibitors (INSTI). We examine the risk of CVD in PLWH on INSTI-based regimens. Methods: Using Truven Health Analytics MarketScan® databases for commercially insured and Medicaid covered adults, we identified PLWH newly initiated on ART between Jan 1, 2008 and Dec 30, 2015. New users were those without ART claims in the 6 months prior to study inclusion. The primary outcome, major adverse cardiac event (MACE), was a composite of acute MI, ischemic stroke, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) assessed through Dec 30, 2016. We excluded PLWH with MACE events 6 months prior to the first stable regimen start. We identified cardiac outcomes and covariates associated with risk of cardiac events using ICD-9-CM diagnosis and procedure codes and CPT-4 codes. Calendar-time specific probability-weighted Cox proportional hazards models were used to estimated hazard ratios (HR) and 95% confidence intervals (CI) for association between INSTI use and MACE. Propensity score models included potential predictors of CVD and INSTI use. Censoring occurred for the earliest of MACE events during the first 6 months of a stable regimen, 90 days post-ART switch, health plan disenrollment, death and study end. Results: 20,459 new ART initiators were identified. 5,128 (25%) PLWH initiated INSTI-based regimens (raltegravir 33%, elvitegravir 49%, dolutegravir 18%). 11,191 (55%) initiated non-nucleoside reverse transcriptase inhibitors and 4,145 (20%) protease inhibitors. Median duration of follow-up was 561 (348, 985) days. Mean age was 40.6 years, 79% were male, and 17% were Medicaid insured. Hypertension was present in 9.5% of INSTI users vs 7.4% non-users; lipid lowering treatment in 19.8% vs 17.9%; diabetes in 6% vs 4.8% and smoking in 13.5% vs 10.2%. 161 MACE events occurred; acute MI 11 (0.21%) vs 55 (0.36%), stroke 14 (0.27%) vs 48 (0.31), CABG 1 (0.02%) vs 6 (0.04%), PCI 5 (0.1%) vs 21 (0.14%) of INSTI users vs. non-users. INSTI-based ART was associated with significantly lower risk of MACE events (HR 0.57; 95% CI 0.45, 0.73) compared to non-INSTI based regimens. Conclusion: INSTI-based regimens were associated with a 43% decreased risk of CVD in this cohort. Validation of these findings in cohorts with longer follow up is needed.

Lower Cardiovascular Disease Risk Associated with Integrase Inhibitors

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Background

- People living with HIV (PLWH) are at greater risk of cardiovascular disease (CVD) with increased rates of traditional risk factors for CVD, effects from HIV infection itself and antiretroviral therapy (ART) exposure, all thought to be contributing factors.
- Previous studies have demonstrated increased CVD risk associated with protease inhibitors as well as the NRTI, abacavir.
- No studies have examined CVD in PLWH on integrase strand transfer inhibitors (INSTI).

Aims

To examine the risk of CVD in PLWH on INSTI-based regimens.

Methods

- Using Truven Health Analytics MarketScan® databases for commercially insured and Medicaid covered adults, we identified PLWH newly initiated on ART between Jan 1, 2008 and Dec 30, 2015.
- New users were those with at least six months enrollment prior to study initiation of stable ART.
- The primary outcome, major adverse cardiac event (MACE), was a composite of acute myocardial infarction (MI), ischemic stroke, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). We excluded PLWH with MACE events 6 months prior to the start of the first stable regimen.
- We identified cardiac outcomes and covariates associated with risk of cardiac events identified with ICD-9-CM diagnosis and procedure codes and CPT-4 codes.
- Calendar-time specific (two year increments) probability-weighted Cox proportional hazards models were used to estimated hazard ratios (HR) and 95% confidence intervals (CI) for association between INSTI use and MACE.
- Balance between the weighted groups was assessed using standardized difference.
- Propensity score models included potential predictors of CVD and INSTI use including underlying co-morbidities, CVD medications, age and gender.
- Individuals were censored for the earliest of: MACE events during the first six months of a stable regimen or 90 days post-ART switch, health plan disenrollment, death or study end (December 30, 2016).

Results

- 20,459 new ART initiators were identified. 5,128 (25%) initiated INSTI-based regimens (raltegravir 33%, elvitegravir 49%, dolutegravir 18%).
- 11,191 (55%) initiated non-nucleoside reverse transcriptase inhibitors and 4,145 (20%) initiated protease inhibitors.
- Median duration of follow-up was 561 (IQR 348, 985) days.
- Mean age was 40.6 years, 79% were male, and 17% were Medicaid insured.

Table 1. Baseline study characteristics

Characteristics	Non-INSTI n=15,331	INSTI n=5,128
Age in years (mean, SD)	40.8 (10.8)	39.9 (11.4)
Males	12,112 (79.0)	4,092 (79.8)
Medicaid insured	2,410 (15.7)	1,023 (20.0)
Hypertension	1,127 (7.4)	489 (9.5)
Diabetes mellitus	733 (4.8)	306 (6.0)
Tobacco use	1,563 (10.2)	694 (13.5)
Lipid lowering therapy	2,742 (17.9)	1,015 (19.8)
Drug use	292 (1.9)	145 (2.8)
Hepatitis B infection	292 (1.9)	131 (2.6)
Hepatitis C infection	621 (4.1)	568 (11.1)
Depression	411 (2.7)	195 (3.8)

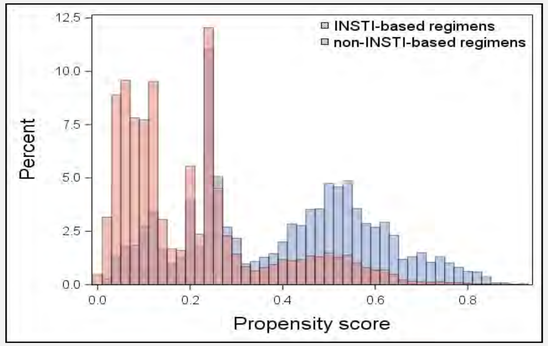
INSTI, integrase strand transfer inhibitor; SD, standard deviation. All standardized mean differences were <0.1.

Table 2. Major adverse cardiac event outcomes

Outcomes	Non-INSTI n=15,331	INSTI n=5,128
Overall MACE	130 (0.85)	31 (0.60)
Acute myocardial infarction	55 (0.36%)	11 (0.21%)
Stroke	48 (0.31)	14 (0.27%)
Coronary artery bypass	6 (0.04%)	1 (0.02%)
Percutaneous coronary intervention	21 (0.14%)	5 (0.10%)

INSTI, integrase strand transfer inhibitor; MACE, major adverse cardiac event

Figure 1. Distribution of the propensity score for INSTI-based regimen in the population

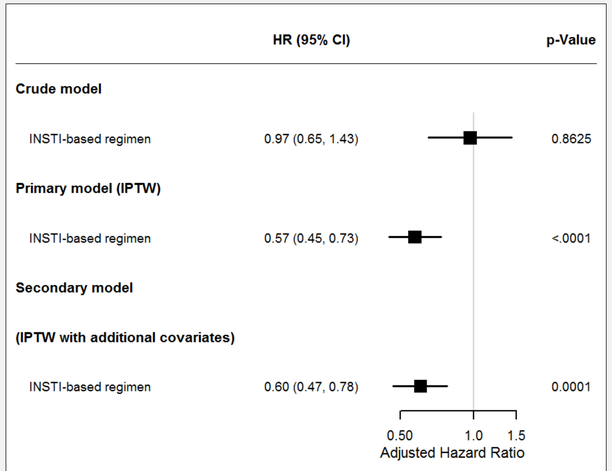


In the primary weighted model that included only exposure to INSTI, INSTI-based ART was associated with significantly lower risk of MACE events (HR 0.57; 95% CI 0.45, 0.73) compared to persons treated with non-INSTI based regimens.

The result remained significant in a sensitivity analysis that included additional factors associated with MACE.

Results

Figure 2. Inverse probability of treatment weighted model for overall MACE events with additional sensitivity analysis



MACE, major adverse cardiac event; IPWT, inverse probability of treatment weighted; INSTI, integrase strand transfer inhibitor. Additional variables included in the secondary model included year of INSTI initiation, Medicaid payer, age, gender, congestive heart failure, diabetes, diagnosis or treatment of lipid abnormality, chronic pulmonary disease, anemia, depression, liver disease, lymphoma, renal failure, hepatitis , sickle cell, atrial fibrillation, smoking/smoking related disease

Conclusions

- INSTI-based regimens were significantly associated with a 43% decreased risk of CVD in this cohort
- The results did not change appreciably in a sensitivity analysis with additional covariates
- Validation of these findings in cohorts with longer follow up is needed

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