

Online Resource 2

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Report-level comparator-definition sensitivity in FAERS cardiometabolic disproportionality analysis:

A long-acting cabotegravir/rilpivirine HIV pharmacovigilance case study

Authors:

Shigeru Hasebe^{1*}, Chihiro Nishikawa¹, Yuki Miura¹, Taiki Kusaka¹, Masayuki Tanaka², Shiori Iwane²,

Toshikazu Tsuji², Hiroyuki Kushida³, Maho Kikuta^{1*}

Affiliations:

1 Department of Social Pharmacy, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1

Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan.

2 Laboratory of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1

Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan.

3 Department of Pharmacy, National Hospital Organization Osaka Minami Medical Center, 2-1

Kidohigashi-machi, Kawachinagano, Osaka 586-8521, Japan.

Corresponding authors:

Shigeru Hasebe and Maho Kikuta are co-corresponding authors.

Shigeru Hasebe, Department of Social Pharmacy, Faculty of Pharmaceutical Sciences, Setsunan

University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan; E-mail:

shigeru.hasebe@setsunan.ac.jp

Maho Kikuta, Department of Social Pharmacy, Faculty of Pharmaceutical Sciences, Setsunan

University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan; Tel: +81-72-866-3248; E-mail:

kikuta@pharm.setsunan.ac.jp

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Supplementary Methods

Overview. The main manuscript describes the core study design, data source, report-level proxy cohort construction, outcome domains, report-level covariates, and primary statistical analyses. This Online Resource provides operational definitions, balance diagnostics, non-IPTW sensitivity outputs, geographic summaries, regimen-plus composition, negative control outcome analysis, exploratory subgroup analyses, and quarterly reporting-volume summaries. All definitions are report-level operational definitions for pharmacovigilance signal characterization and should not be interpreted as adjudicated clinical endpoints, incident diagnoses, complete clinical histories, patient-level treatment status, or longitudinal treatment histories.

Data source and verification limits

The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) public quarterly files contain structured report fields, verbatim drug product entries, therapy date records when available, and adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA). FAERS is a spontaneous reporting system containing reports of suspected adverse events. Reports are not independently adjudicated, exposure denominators are unavailable, and the existence of a report does not establish that a listed drug caused the reported event. Therefore, results presented in this Online Resource should be interpreted as hypothesis-generating reporting patterns for pharmacovigilance signal characterization, not

as incidence, clinical risk, or causal comparative safety estimates.

Study window and market restriction

FAERS quarterly files downloaded on September 7, 2025, were analyzed for 2022 Q1 through 2025 Q2.

Analyses were restricted to reports from the study-defined reporting-market set after an approximately one-year post-approval lag for long-acting cabotegravir/rilpivirine (CAB/RPV). The country/region list is provided in Supplementary Table S2. Residual calendar-time effects, including delayed implementation of long-acting injectable therapy and stimulated reporting, cannot be excluded.

Cohort definitions (report-level proxies)

Cohorts were defined using report-level antiretroviral therapy (ART)-listing proxies as specified in the main manuscript. CAB/RPV case-application reports listed both cabotegravir and rilpivirine. Oral integrase strand transfer inhibitor (INSTI) proxy comparators were restricted to the three study-defined complete oral regimens listed below. Oral comparator reports listing only one such complete regimen were classified as regimen-only; those with additional antiretroviral entries elsewhere in the same report were classified as regimen-plus. Regimen-plus versus regimen-only served as an internal report-level proxy-comparator contrast. Co-listed antiretroviral entries may reflect prior therapy, treatment switching, possible concomitant use, case-version updates, or reporting practices; they do not establish treatment sequence,

adherence, concomitant exposure, treatment duration, treatment phase, or patient-level regimen composition.

Covariates and reporter type

Report-level covariates were limited to age, sex, and reporter type. Age was categorized as <40 years, 40–59 years, ≥ 60 years, or unknown. Reporter type was derived from the FAERS reporter-occupation field and classified as healthcare professional, non-healthcare professional, or unknown. When multiple reporter-occupation codes were present, any healthcare professional code classified the report as healthcare professional. Missing or blank reporter-occupation values were coded as unknown.

Missing data

Missing or blank values for age, sex, and reporter type were retained as unknown categories in the main analyses; the main analyses were not complete-case analyses. Stratified analyses were restricted to reports with known values for the relevant stratification variable. Sex-stratified analyses excluded reports with unknown sex, and age-stratified analyses excluded reports with unknown age. Age completeness by cohort is shown in Table 1 of the main manuscript.

Scope of Original index oral regimens

The Original index oral regimens were limited to bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC), dolutegravir plus tenofovir alafenamide/emtricitabine (DTG+TAF/FTC), and dolutegravir/lamivudine (DTG/3TC). TDF-based INSTI regimens were not included in the Original index definitions. For the post-review TDF-inclusive reconstruction, dolutegravir plus TDF/emtricitabine and dolutegravir plus TDF/lamivudine were added as eligible index regimens, as described in the Main Methods and Supplementary Tables S11–S12.

Outcome-specific eligibility restrictions

For each cardiometabolic outcome, the same outcome-specific MedDRA term set used to identify target-event reporting in REAC_PT was also applied to INDI_PT. A report was excluded from the eligible population for a given outcome when INDI_PT contained a term from the corresponding outcome-specific set. The restriction was applied separately for 3-point MACE-related reporting, expanded MACE-related reporting, diabetes-related reporting, dyslipidemia-related reporting, and hypertension-related reporting. Accordingly, the outcome-specific eligible denominators could differ across analyses. This procedure was intended to reduce reports in which the target condition was already represented as an indication within the same report; it did not establish clinical onset, first-ever occurrence, or incident disease. The outcome-specific MedDRA term sets used for event identification and indication-based exclusion are provided in

Supplementary Table S1.

Statistical approach and diagnostics, including negative control outcome

Balance diagnostics were assessed using standardized mean differences (SMDs) before and after inverse probability of treatment weighting (IPTW) and are provided in Supplementary Table S3. Adjusted reporting odds ratios (aRORs) were estimated in the main analyses using IPTW-weighted logistic regression with Huber-White robust standard errors, as described in the main manuscript. If any measured balance variable remained imbalanced after weighting (post-IPTW $|SMD| \geq 0.1$), that variable was additionally included in the corresponding IPTW-weighted outcome model. A non-IPTW covariate-adjusted logistic regression sensitivity analysis for 3-point MACE-related reporting is provided in Supplementary Table S4. The study-defined negative control outcome analysis is presented in Supplementary Figure S1 and should be interpreted as a residual-bias diagnostic, not as proof that residual bias or confounding was absent. No binary aROR threshold was used to define a signal.

Supplementary Table S1. MedDRA-based outcome definitions and term lists used in the analysis.

Notes: Outcomes were operationalized using MedDRA version 28.1. A report met an outcome definition if at least one listed term was recorded. Outcomes were not mutually exclusive. Concordance between the listed terms and the analytical code was checked as part of the technical quality-assurance process. These definitions were used for report-level pharmacovigilance analyses and did not constitute clinically adjudicated endpoints, validated clinical diagnoses, incident events, or complete medical histories.

(1) Definition of 3-point MACE-related reporting

Clinical domain	SMQ / Category	Preferred terms	Notes
Myocardial infarction / Coronary events	Ischaemic heart disease SMQ	Myocardial infarction, Acute myocardial infarction, Angina pectoris, Coronary artery disease, Coronary artery occlusion, Coronary arterial stent insertion, Coronary artery bypass, Troponin increased, Acute coronary syndrome, Angina unstable, Arteriosclerosis coronary artery, Acute cardiac event, Blood creatine phosphokinase abnormal, Myocardial ischaemia, Ischaemic cardiomyopathy, Coronary artery stenosis, Angioplasty	Includes acute coronary syndromes, thrombosis, procedural interventions, and biomarker events routinely used to identify myocardial ischaemic outcomes.
Cerebrovascular events	Central nervous system vascular disorders SMQ	Cerebral infarction, Ischaemic stroke, Cerebrovascular accident, Transient ischaemic attack, Cerebral haemorrhage, Cerebral ischaemia, Cerebral thrombosis, Cerebral artery occlusion, Cerebral venous thrombosis, Cerebrovascular disorder, Haemorrhagic stroke, Subarachnoid haemorrhage, Subdural haemorrhage, Brain stem haemorrhage, Thalamus haemorrhage, Intracranial haemorrhage neonatal, Intraventricular	Includes ischaemic and haemorrhagic stroke events, thrombotic and embolic cerebrovascular events, vascular malformations, and related cerebrovascular complications.

		haemorrhage, Reversible cerebral vasoconstriction syndrome, Stroke in evolution, Carotid artery occlusion, Carotid artery stenosis, Carotid artery disease, Embolic cerebellar infarction, Cerebellar infarction, Cerebellar haemorrhage, Intracranial aneurysm, Hydrocephalus	
Other vascular / neurological events		Balance disorder, Hemiparesis, Hyperaesthesia, Hypoxic-ischaemic encephalopathy, Spinal cord haemorrhage, Spinal epidural haematoma, Arterial stenosis, Arteriosclerosis	These events are not classical myocardial or cerebrovascular events, but are clinically considered related to ischaemic or vascular neurological outcomes in a pharmacovigilance context.
Cardiovascular death	Fatal outcomes (custom set)	Cardiovascular death, Cardiac death, Sudden cardiac death, Cardiac arrest, Cardio-respiratory arrest	To enhance the sensitivity of capturing fatal cardiovascular events, a study-defined custom set of PTs was used, as SMQ-based searches may not sufficiently identify all relevant fatal outcomes reported in FAERS.

(2) Definition of expanded MACE-related reporting

Clinical domain	SMQ / Category	Preferred terms	Notes
Myocardial infarction / Coronary events	Ischaemic heart disease SMQ	Same as the 3-point MACE-related reporting definition	Included as part of the 3-point MACE-related reporting definition.
Cerebrovascular events	Central nervous system vascular	Same as the 3-point MACE-related reporting definition	Included as part of the 3-point MACE-related

	disorders SMQ		reporting definition.
Other vascular / neurological events		Same as the 3-point MACE-related reporting definition	Included as part of the 3-point MACE-related reporting definition.
Cardiovascular death	Fatal outcomes (custom set)	Same as the 3-point MACE-related reporting definition	Included as part of the 3-point MACE-related reporting definition.
Cardiac failure-related events	Cardiac failure SMQ	Cardiac failure; Cardiac failure acute; Cardiac failure congestive; Left ventricular failure; Right ventricular failure; Pulmonary oedema; Cor pulmonale; Shock; Cardiogenic shock; Ejection fraction decreased; Heart failure with reduced ejection fraction	New domain added beyond the 3-point MACE-related reporting definition. These terms capture reports coded with cardiac failure-related Preferred Terms and are intended for pharmacovigilance reporting-pattern characterization.

(3) Definition of diabetes-related reporting

Clinical domain	SMQ / Category	Preferred terms	Notes
Diabetes mellitus / Glycaemic disorders	Hyperglycaemia / Diabetes SMQ	Diabetes mellitus; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Steroid diabetes; Gestational diabetes; Diabetes mellitus inadequate control; Diabetic ketoacidosis; Ketoacidosis; Diabetic coma; Impaired fasting glucose; Glucose tolerance impaired; Glycosuria; Glucose urine present; Blood glucose increased; Blood glucose decreased; Glycosylated haemoglobin increased; Glycosylated haemoglobin abnormal; Urine ketone body present; Hypoglycaemia; Hypoglycaemia neonatal; Seizure	Captures reports coded with diabetes-related, glycaemic-disorder, metabolic-decompensation, or laboratory-abnormality terms. These terms are intended for pharmacovigilance signal characterization, and do not establish new-onset diabetes, incident

			glycaemic disease, or a clinical diagnosis.
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(4) Definition of dyslipidemia-related reporting

Clinical domain	SMQ / Category	Preferred terms	Notes
Dyslipidaemia / Lipid metabolism disorders	Hyperlipidaemia / Dyslipidaemia SMQ	Hypertriglyceridaemia; Hyperlipidaemia; Low density lipoprotein increased; Dyslipidaemia; Lipids abnormal; Blood triglycerides increased; Hypercholesterolaemia; Blood cholesterol increased; Blood cholesterol abnormal; Lipids increased; High density lipoprotein decreased; Lipoprotein abnormal; Blood triglycerides abnormal; Type V hyperlipidaemia; Blood cholesterol decreased; Blood triglycerides decreased; High density lipoprotein increased; High density lipoprotein abnormal	Captures reports coded with lipid-disorder diagnoses or lipid-related laboratory abnormalities. These terms are intended for reporting-pattern characterization, and do not establish incident dyslipidemia or validated lipid outcomes.

(5) Definition of hypertension-related reporting

Clinical domain	SMQ /Category	Preferred terms	Notes
Hypertension and blood pressure disorders	Hypertension SMQ / Vascular disorders	Hypertension; Hypertension essential; Hypertension malignant; Hypertension neonatal; Hypertension pulmonary; Blood pressure increased; Blood pressure abnormal; Diastolic hypertension; Systolic hypertension; Hypertensive crisis; Hypertensive emergency; Hypertensive encephalopathy; Secondary hypertension; White coat hypertension	Includes clinical diagnosis terms, hypertension subtypes, and blood-pressure measurement-related abnormalities. These terms are intended for pharmacovigilance reporting definitions, and do not establish incident hypertension or

			longitudinal blood-pressure status.
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(6) Definition of the negative control outcome

Clinical domain	SMQ / Category	Preferred terms	Notes
Minor soft-tissue injury	Injury, poisoning and procedural complications SOC Soft-tissue trauma category	Fall Contusion Muscle contusion Aponeurosis contusion Ankle sprain	A composite negative control outcome defined as a set of minor soft-tissue injury events considered biologically unrelated to antiretroviral exposure or cardiovascular outcomes. Events were selected a priori from MedDRA v28.1 and restricted to peripheral soft-tissue injuries to minimize confounding from disease-related pathophysiology.
Excluded severe or unrelated injuries		Bone contusion; Brain contusion; Cardiac contusion; Eye contusion Eyelid contusion; Gastrointestinal organ contusion; Genital contusion; Kidney contusion; Liver contusion Oral contusion; Pancreatic contusion; Pharyngeal contusion; Pulmonary contusion; Spleen contusion; Post procedural contusion	Reports co-listing any of these excluded terms were removed from the NCO definition to reduce overlap with more severe injuries or distinct etiologies. This exclusion was applied at the report level, and does not imply event chronology or prior history.

Notes: The negative control outcome was used as a limited bias diagnostic. It did not validate the analytical framework or exclude residual confounding.

Abbreviations: MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; NCO, negative control outcome; PT, Preferred Term; SMQ, Standardised MedDRA

Query; SOC, System Organ Class.

Supplementary Table S2. Countries and regions included in the study-defined reporting-market set.

Country code	Country name	Region
US	United States	North America
CA	Canada	
PR	Puerto Rico	
DE	Germany	Europe
FR	France	
GB	United Kingdom	
PT	Portugal	
ES	Spain	
BE	Belgium	
LT	Lithuania	
CH	Switzerland	
LV	Latvia	
AT	Austria	
IT	Italy	
CZ	Czech Republic	
IE	Ireland	
FI	Finland	
SE	Sweden	
PL	Poland	
RO	Romania	
UA	Ukraine	
GR	Greece	
NL	Netherlands	
DK	Denmark	
SI	Slovenia	
LU	Luxembourg	
HR	Croatia	
SK	Slovakia	
BG	Bulgaria	
EU	European Union (Unspecified)	
JP	Japan	Asia-Pacific
KR	South Korea	
CN	China	

TW	Taiwan	
AU	Australia	
SG	Singapore	
TR	Turkey	
RU	Russia	
MX	Mexico	Latin America
AR	Argentina	
BR	Brazil	
GF	French Guiana	
SA	Saudi Arabia	Middle East / Africa
ZA	South Africa	
RE	Réunion	

Notes: This table lists the countries and regions included in the study-defined reporting-market set. Country or region was derived from the FAERS country/region field. Reports from locations outside this set and reports with missing or uninformative country/region values were excluded as described in the Supplementary Methods. The study-defined set should not be interpreted as an official ICH country classification or as evidence of uniform adverse-event-reporting coverage across the included locations.

Abbreviations: FAERS, U.S. Food and Drug Administration Adverse Event Reporting System; US, United States.

Supplementary Table S3. Submitted Original standardized mean differences before and after inverse probability of treatment weighting.

Notes: This table reproduces the covariate-balance results from the submitted Original analyses. SMDs are shown before and after IPTW for measured report-level characteristics. Absolute SMD values below 0.1 were considered indicative of acceptable measured balance. These diagnostics did not establish absence of residual confounding or clinical exchangeability. The post-review analyses of ESS, weights, and PS overlap are reported separately in Supplementary Table S10 and Supplementary Figure S5.

(1) SMDs for primary and secondary outcome analyses

Variable	3-point MACE-related		Expanded MACE-related		Diabetes-related		Dyslipidemia-related		Hypertension-related		Negative control outcome	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Regimen-plus vs. regimen-only												
Age	0.447	0.050	0.448	0.050	0.435	0.049	0.450	0.050	0.454	0.053	0.448	0.048
Sex	0.354	0.067	0.354	0.068	0.353	0.069	0.356	0.073	0.361	0.072	0.355	0.065
Reporter type	0.764	0.017	0.766	0.017	0.761	0.019	0.769	0.013	0.775	0.010	0.757	0.018
Pre-existing condition indicators												
Diabetes mellitus	0.001	0.025	0.001	0.024	—	—	0.016	0.015	0.032	0.031	0.004	0.023
Dyslipidemia	0.010	0.002	0.088	0.002	0.090	0.002	—	—	0.050	0.001	0.095	0.002

Hypertension	0.100	0.013	0.094	0.015	0.095	0.015	0.001	0.001	—	—	0.104	0.015
CAB/RPV vs. regimen-plus												
Age	0.786	0.160	0.786	0.158	0.807	0.159	0.809	0.134	0.798	0.155	0.787	0.156
Sex	0.628	0.211	0.628	0.212	0.636	0.230	0.637	0.223	0.638	0.167	0.628	0.208
Reporter type	1.652	0.326	1.655	0.321	1.664	0.297	1.676	0.279	1.668	0.354	1.640	0.319
Pre-existing condition indicators												
Diabetes mellitus	0.086	0.262	0.033	0.242	—	—	0.052	0.011	0.077	0.515	0.026	0.248
Dyslipidemia	0.049	0.027	0.041	0.040	0.135	0.108	—	—	0.010	0.028	0.055	0.025
Hypertension	0.154	0.151	0.147	0.140	0.146	0.156	0.001	0.001	—	—	0.160	0.157
CAB/RPV vs. regimen-only												
Age	0.349	0.013	0.348	0.013	0.367	0.015	0.364	0.012	0.354	0.010	0.350	0.013
Sex	0.276	0.003	0.276	0.003	0.284	0.003	0.282	0.004	0.279	0.005	0.275	0.003
Reporter type	0.677	0.052	0.678	0.052	0.687	0.055	0.688	0.051	0.677	0.048	0.676	0.051
Pre-existing condition indicators												
Diabetes mellitus	0.033	0.010	0.033	0.010	—	—	0.068	0.004	0.046	0.008	0.031	0.009
Dyslipidemia	0.047	0.011	0.049	0.013	0.052	0.024	—	—	0.050	0.005	0.042	0.008
Hypertension	0.059	0.020	0.058	0.020	0.057	0.034	0.001	0.001	—	—	0.062	0.022

(2) SMDs for sex-stratified subgroup analyses of 3-point MACE-related reporting

Variable	Male			Female	
	Before	After		Before	After
Regimen-plus vs. regimen-only					
Age	0.385	0.026		0.341	0.005
Reporter type	0.745	0.050		0.829	0.067
Pre-existing condition indicators					
Diabetes mellitus	0.061	0.046		0.017	0.022
Dyslipidemia	0.014	0.006		0.058	0.023
Hypertension	0.113	0.013		0.123	0.002
CAB/RPV vs. regimen-plus					
Age	0.633	0.129		0.615	0.050
Reporter type	1.684	0.437		1.810	0.495
Pre-existing condition indicators					
Diabetes mellitus	0.101	0.405		0.086	0.053
Dyslipidemia	0.002	0.038		0.113	0.099
Hypertension	0.129	0.189		0.148	0.083
CAB/RPV vs. regimen-only					
Age	0.287	0.019		0.305	0.008
Reporter type	0.726	0.074		0.706	0.099
Pre-existing condition indicators					
Diabetes mellitus	0.079	0.003		0.070	0.009
Dyslipidemia	0.113	0.003		0.063	0.005
Hypertension	0.115	0.041		0.029	0.004

(3) SMDs for age-stratified subgroup analyses of 3-point MACE-related reporting

Variable	Younger Adults		Middle-Aged Adults		Older Adults	
	Before	After	Before	After	Before	After
Regimen-plus vs. regimen-only						
Sex	0.190	0.099	0.139	0.009	0.148	0.027
Reporter type	0.900	0.087	0.740	0.006	0.590	0.074
Pre-existing condition indicators						
Diabetes mellitus	0.020	0.024	0.053	0.009	0.010	0.032
Dyslipidemia	0.047	0.001	0.036	0.025	0.135	0.003
Hypertension	0.148	0.010	0.078	0.039	0.127	0.009
CAB/RPV vs. regimen-plus						
Sex	0.285	0.259	0.178	0.045	0.169	0.024
Reporter type	1.630	0.256	1.735	0.823	0.942	0.081
Pre-existing condition indicators						
Diabetes mellitus	0.035	0.003	0.017	0.385	0.025	0.064
Dyslipidemia	0.123	0.310	0.258	0.312	0.190	0.019
Hypertension	0.175	0.309	0.053	0.271	0.107	0.006
CAB/RPV vs. regimen-only						
Sex	0.130	0.027	0.051	0.007	0.120	0.005
Reporter type	0.539	0.032	0.767	0.147	0.350	0.008
Pre-existing condition indicators						
Diabetes mellitus	0.055	0.003	0.283	0.014	0.015	0.002
Dyslipidemia	0.012	0.001	0.281	0.020	0.062	0.020
Hypertension	0.038	0.001	0.012	0.094	0.021	0.007

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; IPTW, inverse probability of treatment

weighting; MACE, major adverse cardiovascular events; SMD, standardized mean difference.

Diabetes mellitus	1.46	(0.72–2.93)	0.2922	0.33	(0.07–1.52)	0.1542	1.12	(0.56–2.24)	0.7391
Dyslipidemia	1.24	(0.62–2.47)	0.5433	2.76	(1.20–6.34)	0.0172*	2.78	(1.53–5.07)	0.0008**
Hypertension	1.99	(1.16–3.42)	0.0131*	1.96	(0.89–4.31)	0.0957	2.23	(1.28–3.92)	0.0049**

Notes: This table presents the Original covariate-adjusted logistic regression analyses without IPTW. Cohort coefficients are expressed for the first-listed report stratum relative to the second-listed stratum. Covariate estimates are shown for transparency and should not be interpreted as clinical risk-factor effects. Directional similarity between this analysis and an IPTW analysis was not interpreted as evidence of robustness or clinical validity. P values were descriptive and were not used to define disproportionality signals.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; FAERS, U.S. Food and Drug Administration Adverse Event Reporting System; HCP, healthcare professional; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table S5. Geographic composition of the Original report strata.

Cohort	US		non-US	
	n	(%)	n	(%)
Regimen-plus	3,916	(88.3%)	518	(11.7%)
Regimen-only	10,791	(74.1%)	3,768	(25.9%)
CAB/RPV	8,506	(84.4%)	1,576	(15.6%)

Notes: Geographic origin was derived from the FAERS country/region field. Non-US reports were reports from locations in the study-defined reporting-market set other than the United States. This table describes report-level geographic composition and should not be interpreted as market share, treatment uptake, or complete adverse-event-reporting coverage.

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; FAERS, U.S. Food and Drug Administration Adverse Event Reporting System; US, United States.

Supplementary Table S6. Report-level co-listed antiretroviral entry classes in the regimen-plus stratum.

Co-listed antiretroviral entry class	Regimen-plus reports with ≥ 1 co-listed entry in the class	
	n	(%)
Reports with ≥ 1 co-listed INSTI entry	2,823	(63.7%)
Reports with ≥ 1 co-listed NNRTI entry	3,203	(72.2%)
Reports with ≥ 1 co-listed PI entry	1,203	(27.1%)
Reports with ≥ 1 co-listed NRTI entry	4,057	(91.5%)
Reports with ≥ 1 co-listed other ARV-class entry	282	(6.4%)

Notes: Categories were not mutually exclusive, and multiple entries within the same class were counted once per report. These data describe report-level co-listing only. Co-listed entries could reflect prior therapy, treatment switching, overlapping or duplicate documentation, possible concurrent use, or reporting practices. They did not establish treatment sequence, confirmed co-administration, adherence, treatment phase, or clinical regimen complexity.

Report-level stratum definition: regimen-plus, reports containing a complete index oral antiretroviral regimen listing together with additional antiretroviral entries.

Abbreviations: ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor.

Supplementary Table S7. Complete-case analyses across the three report-level contrasts and five cardiometabolic outcomes.

Outcome	First-listed events/N	Second- listed events/N	aROR (95% CI)	Max post- IPTW SMD	Min group- specific ESS, %	Max weight
CAB/RPV vs regimen-plus						
3-point MACE	61/3,964	42/3,196	0.82 (0.51–1.33)	0.398	17.6	38.8
Expanded MACE	63/3,963	47/3,192	0.69 (0.43–1.08)	0.400	17.4	39.0
Diabetes	31/3,858	31/3,178	0.55 (0.27–1.12)	0.423	16.3	39.4
Dyslipidemia	13/3,861	60/3,150	0.09 (0.04–0.18)	0.433	15.7	40.6
Hypertension	56/3,920	64/3,129	0.53 (0.31–0.91)	0.399	17.3	38.6
Regimen-plus vs regimen-only						
3-point MACE	42/3,196	152/7,936	0.97 (0.66–1.44)	0.045	76.7	2.6
Expanded MACE	47/3,192	196/7,931	0.90 (0.63–1.30)	0.045	76.6	2.6
Diabetes	31/3,178	95/7,900	1.52 (0.97–2.38)	0.044	76.7	2.6
Dyslipidemia	60/3,150	91/7,895	3.27 (2.28–4.67)	0.047	76.3	2.6
Hypertension	64/3,129	216/7,867	1.16 (0.84–1.60)	0.048	76.3	2.6
CAB/RPV vs regimen-only						
3-point MACE	61/3,964	152/7,936	0.94 (0.68–1.30)	0.067	74.6	6.7
Expanded MACE	63/3,963	196/7,931	0.73 (0.53–1.00)	0.067	74.5	6.7
Diabetes	31/3,858	95/7,900	0.73 (0.46–1.17)	0.075	72.7	6.9
Dyslipidemia	13/3,861	91/7,895	0.29 (0.15–0.54)	0.075	72.5	7.0
Hypertension	56/3,920	216/7,867	0.54 (0.39–0.76)	0.065	74.7	6.7

Notes: Complete-case analyses were restricted to reports with known age and sex. Propensity scores were re-estimated separately for each outcome and report-level contrast. Because retention differed substantially across report strata, the complete-case analyses were interpreted as sensitivity analyses for demographic completeness rather than as correction of missing-data bias. First-listed and second-listed correspond to the order of the report strata named in each bold contrast heading. Events/N denotes the number of outcome reports divided by the number of outcome-specific eligible reports.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; PS, propensity score; SMD, standardized mean difference.

Supplementary Table S8. HCP-only analyses of CAB/RPV versus regimen-plus across five cardiometabolic outcomes.

Outcome	CAB/RPV events/N	Regimen-plus events/N	aROR (95% CI)	Max SMD	Min ESS	Max weight
3-point MACE	82/7,935	51/686	0.12 (0.09–0.18)	0.035	97.1	1.3
Expanded MACE	84/7,930	61/681	0.10 (0.07–0.15)	0.036	97.0	1.3
Diabetes	64/7,870	21/682	0.27 (0.17–0.45)	0.039	96.9	1.3
Dyslipidemia	18/7,869	69/664	0.02 (0.01–0.03)	0.038	96.9	1.3
Hypertension	76/7,885	33/656	0.20 (0.13–0.31)	0.037	97.4	1.3

Notes: HCP reports were defined using MD, PH, and HP reporter codes. CN, LW, and unknown reporter categories were excluded. Reporter type was not included in the PS model because all included reports were HCP reports. Acceptable balance of measured age and sex did not establish clinical outcome validity or eliminate unmeasured confounding.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; CN, consumer; ESS, effective sample size; HCP, healthcare professional; HP, health professional; IPTW, inverse probability of treatment weighting; LW, lawyer; MACE, major adverse cardiovascular events; MD, physician; PH, pharmacist; PS, propensity score; SMD, standardized mean difference.

Supplementary Table S9. US-only analyses across the three report-level contrasts and five cardiometabolic outcomes.

Outcome	First-listed events/N	Second- listed events/N	aROR (95% CI)	Max post- IPTW SMD	Min group- specific ESS, %	Max weight
CAB/RPV vs regimen-plus						
3-point MACE	66/8,504	29/3,913	1.27 (0.64–2.50)	0.615	7.4	97.6
Expanded MACE	68/8,500	37/3,910	1.09 (0.59–2.01)	0.616	7.4	97.7
Diabetes	43/8,494	20/3,882	0.58 (0.28–1.21)	0.619	7.2	99.8
Dyslipidemia	25/8,494	24/3,863	0.30 (0.12–0.77)	0.608	7.6	96.4
Hypertension	84/8,477	74/3,820	0.64 (0.35–1.17)	0.633	6.8	105.5
Regimen-plus vs regimen-only						
3-point MACE	29/3,913	164/10,779	0.52 (0.34–0.81)	0.075	66.6	5.0
Expanded MACE	37/3,910	197/10,777	0.55 (0.38–0.80)	0.075	66.5	5.0
Diabetes	20/3,882	130/10,732	0.67 (0.36–1.23)	0.072	66.0	5.2
Dyslipidemia	24/3,863	74/10,739	1.18 (0.64–2.15)	0.073	66.7	5.0
Hypertension	74/3,820	153/10,698	1.38 (1.00–1.89)	0.065	65.1	5.4
CAB/RPV vs regimen-only						
3-point MACE	66/8,504	164/10,779	0.55 (0.40–0.77)	0.137	49.1	15.3
Expanded MACE	68/8,500	197/10,777	0.47 (0.34–0.64)	0.137	49.1	15.3
Diabetes	43/8,494	130/10,732	0.52 (0.31–0.88)	0.135	49.4	15.2
Dyslipidemia	25/8,494	74/10,739	0.51 (0.30–0.85)	0.136	49.2	15.3
Hypertension	84/8,477	153/10,698	0.87 (0.63–1.21)	0.134	49.4	15.4

Notes: The US-only analyses were restricted to reports originating from the United States and were conducted as geographic/reporting-context sensitivity analyses. Propensity scores were re-estimated separately within each outcome-specific US-only population and report-level contrast. The CAB/RPV-versus-regimen-plus analyses showed substantial residual imbalance, effective-sample-size depletion, and extreme weights and were therefore not interpreted as US-specific clinical risk estimates. First-listed and second-listed correspond to the order of the report strata named in each bold contrast heading. Events/N

denotes the number of outcome reports divided by the number of outcome-specific eligible reports.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; PS, propensity score; SMD, standardized mean difference; US, United States.

Supplementary Table S10. Integrated propensity-score and weighting diagnostics for CAB/RPV

versus regimen-plus across reporting-context analyses.

Population	Max post-SMD	Min ESS, %	Max weight	Summary
Original	0.261–0.278	31.1–33.7	29.9–32.4	Residual imbalance and ESS depletion
Complete-case	0.398–0.433	15.7–17.6	38.6–40.6	Greater imbalance and severe ESS depletion
HCP-only	0.035–0.039	96.9–97.4	1.29–1.35	Acceptable measured balance
US-only	0.608–0.633	6.83–7.57	96.4–105.5	Severe imbalance and extreme weights

Notes: Ranges are shown across the five outcome-specific analyses. Propensity-score overlap for the 3-point MACE-related analyses is shown graphically in Supplementary Figure S5. Original refers to the post-review diagnostic reanalysis of the Original population and does not replace the submitted Original aROR analysis. Additional covariate adjustment in the weighted outcome model did not restore inadequate propensity-score overlap or correct positivity concerns.

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; ESS, effective sample size; HCP, healthcare professional; IPTW, inverse probability of treatment weighting; PS, propensity score; SMD, standardized mean difference; US, United States.

Supplementary Table S11. Reconstruction and reclassification of the TDF-inclusive report-level**cohorts.**

Report stratum	Original	TDF-inclusive	Change
CAB/RPV	10,082	10,082	0
Regimen-plus	4,434	6,404	+1,970
Regimen-only	14,559	14,103	-456
Total	29,075	30,589	+1,514

Reconstruction component	Reports, n
Existing regimen-only reclassified as regimen-plus	1,034
Newly eligible TDF regimen-only	578
Newly eligible TDF regimen-plus	936

Final regimen-only count: $14,559 - 1,034 + 578 = 14,103$.

Notes: The TDF-inclusive definitions were reapplied to all eligible reports. The reconstructed cohort was not created by simply appending newly eligible TDF-containing reports. Reclassification of existing reports explains why the regimen-only count decreased.

Comparator-definition label: TDF-inclusive, the reconstruction in which eligible TDF-containing oral regimens were included and the report-level definitions were reapplied to all eligible reports.

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; TDF, tenofovir disoproxil fumarate.

Supplementary Table S12. Full formal paired comparison of reconstructed no-TDF and TDF-inclusive definitions.

(A) Formal paired estimates across three report-level contrasts and five cardiometabolic outcomes

Outcome	Reconstructed no-TDF, aROR (95% CI)	TDF-inclusive, aROR (95% CI)
Regimen-plus vs regimen-only		
3-point MACE-related reporting	1.984 (1.656–2.376)	1.479 (1.224–1.787)
Expanded MACE-related reporting	2.009 (1.704–2.369)	1.451 (1.220–1.725)
Diabetes-related reporting	0.825 (0.623–1.092)	1.680 (1.364–2.070)
Dyslipidemia-related reporting	3.068 (2.557–3.682)	3.952 (3.308–4.722)
Hypertension-related reporting	1.226 (1.004–1.497)	1.570 (1.317–1.872)
CAB/RPV vs regimen-plus		
3-point MACE-related reporting	0.238 (0.196–0.289)	0.379 (0.307–0.469)
Expanded MACE-related reporting	0.199 (0.164–0.240)	0.326 (0.265–0.400)
Diabetes-related reporting	0.516 (0.374–0.714)	0.251 (0.193–0.327)
Dyslipidemia-related reporting	0.049 (0.035–0.068)	0.049 (0.035–0.069)
Hypertension-related reporting	0.337 (0.268–0.425)	0.325 (0.261–0.405)
CAB/RPV vs regimen-only		
3-point MACE-related reporting	0.593 (0.488–0.720)	0.627 (0.515–0.764)
Expanded MACE-related reporting	0.493 (0.408–0.596)	0.516 (0.426–0.625)
Diabetes-related reporting	0.373 (0.289–0.481)	0.429 (0.331–0.556)
Dyslipidemia-related reporting	0.138 (0.097–0.197)	0.176 (0.123–0.253)
Hypertension-related reporting	0.440 (0.360–0.537)	0.483 (0.394–0.593)

(B) CAB/RPV versus regimen-plus weighting diagnostic summary

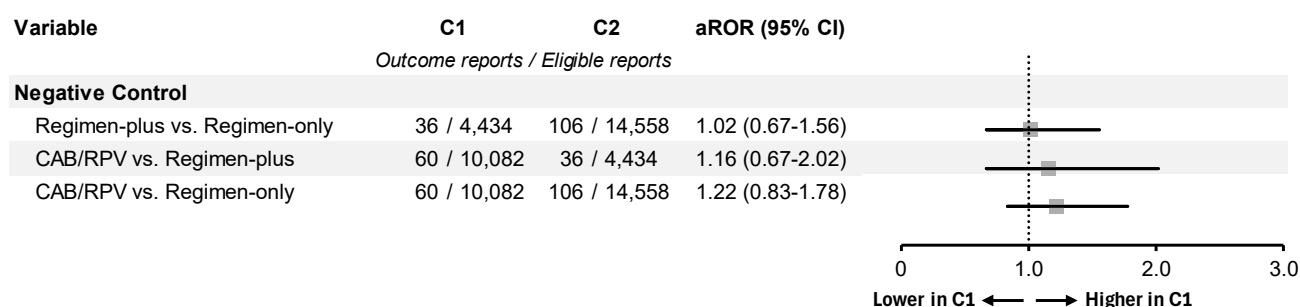
Diagnostic	Reconstructed no-TDF	TDF-inclusive
Maximum post-IPTW SMD	0.318–0.331	0.096–0.101
Minimum group ESS, %	25.4–27.1	58.1–59.3
Maximum weight	8.27–8.92	3.18–3.28

Notes: The reconstructed no-TDF and TDF-inclusive populations were generated using the same formal cohort definitions and reconstruction pipeline. Reconstructed no-TDF refers to the harmonized reference reconstruction excluding eligible TDF-containing oral regimens and was not the submitted Original population. TDF-inclusive refers to the corresponding reconstruction including eligible TDF-containing oral regimens, with the report-level comparator definitions reapplied to all eligible reports. Panel A presents the complete formal paired comparison across the three report-level contrasts and five cardiometabolic outcomes. Panel B summarizes weighting diagnostics across the five CAB/RPV-versus-regimen-plus outcome-specific analyses. Estimates below 1 were not interpreted as protective effects. In the TDF-inclusive hypertension analysis, the maximum post-IPTW SMD was 0.101, and sex was additionally included in the weighted outcome model.

Report-level stratum definitions: Regimen-only denotes reports containing a complete index oral antiretroviral regimen listing without additional antiretroviral entries; regimen-plus denotes reports containing a complete index oral antiretroviral regimen listing together with additional antiretroviral entries. These labels describe report-level listing patterns and do not establish treatment sequence or confirmed concurrent exposure.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; SMD, standardized mean difference; TDF, tenofovir disoproxil

fumarate.

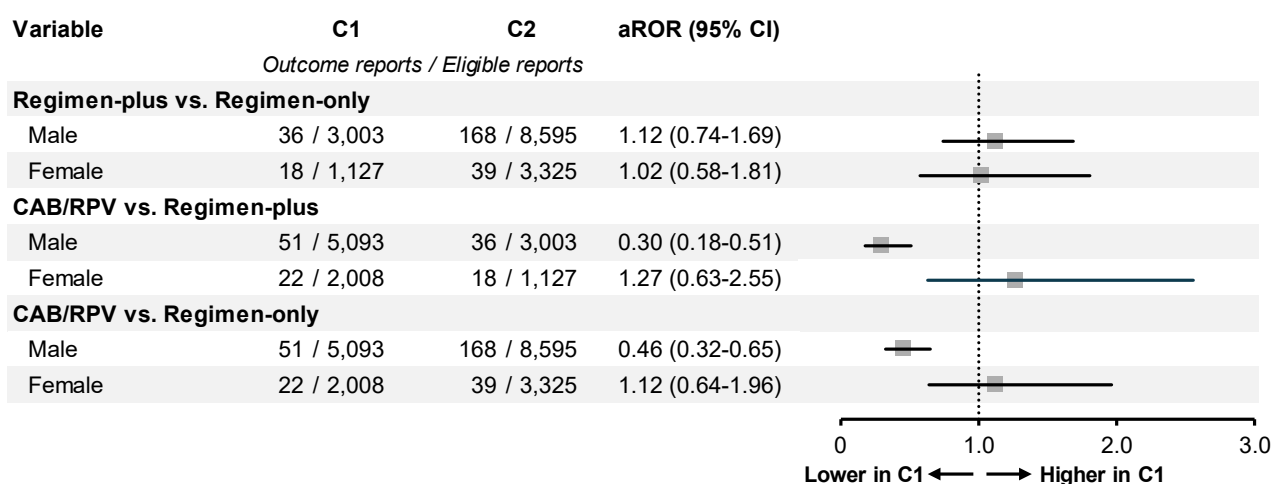


Supplementary Figure S1. Negative control outcome analysis for minor fall-related soft-tissue injury reporting.

The forest plot shows aRORs with 95% CIs for the negative control outcome. C1 and C2 denote the first-listed and second-listed report strata in each contrast, respectively. Counts are shown as outcome reports/eligible reports. The negative control outcome was used as a limited bias diagnostic. Confidence intervals included 1 in all three contrasts; this did not validate the analytical framework or exclude residual confounding.

Contrast labels: C1, first-listed report stratum; C2, second-listed report stratum.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; IPTW, inverse probability of treatment weighting.



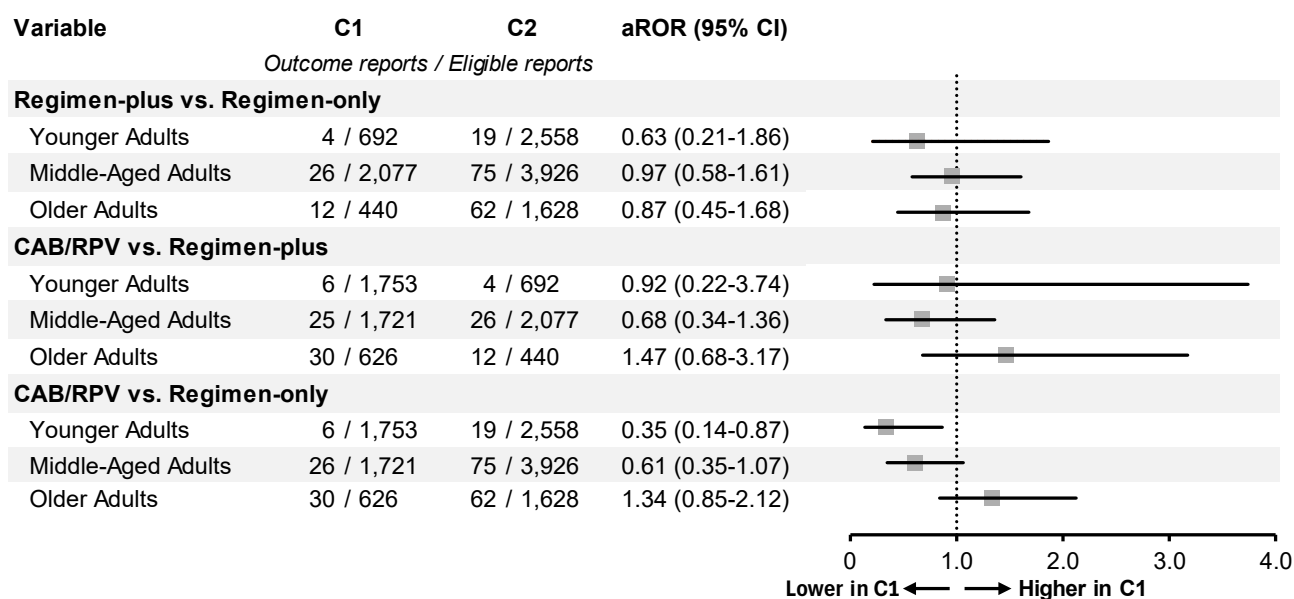
Supplementary Figure S2. Sex-stratified analysis of adjusted reporting odds ratios for 3-point

MACE-related reporting.

The forest plot shows exploratory sex-stratified aRORs with 95% CIs. C1 and C2 denote the first-listed and second-listed report strata in each contrast. Reports with unknown sex were excluded. Estimates were imprecise and did not support sex-specific clinical interpretation.

Contrast labels: C1, first-listed report stratum; C2, second-listed report stratum.

Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; MACE, major adverse cardiovascular events.



Supplementary Figure S3. Age-stratified analysis of adjusted reporting odds ratios for 3-point

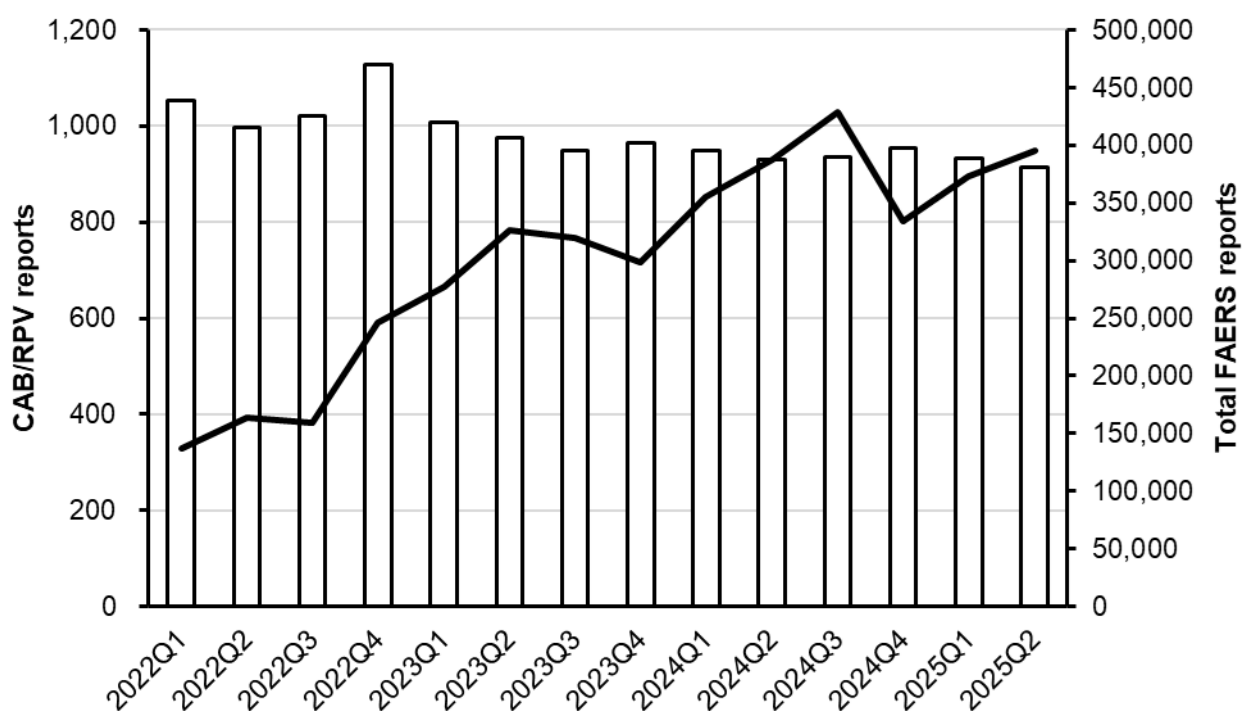
MACE-related reporting.

The forest plot shows exploratory age-stratified aRORs with 95% CIs. C1 and C2 denote the first-listed and second-listed report strata in each contrast. Analyses were restricted to reports with known age.

Estimates were imprecise and did not support age-stratum-specific clinical interpretation.

Contrast labels: C1, first-listed report stratum; C2, second-listed report stratum.

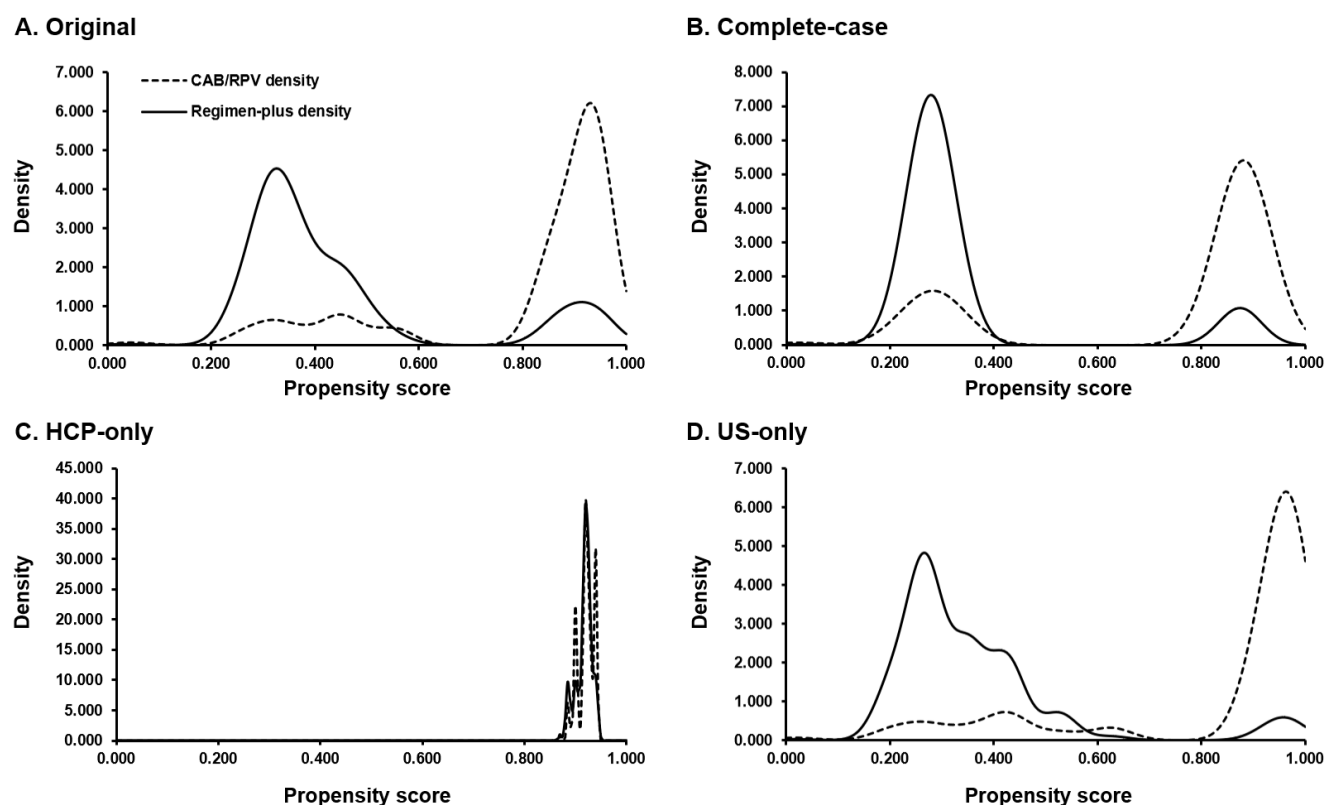
Abbreviations: aROR, adjusted reporting odds ratio; CAB/RPV, long-acting cabotegravir/rilpivirine; CI, confidence interval; MACE, major adverse cardiovascular events.



Supplementary Figure S4. Quarterly CAB/RPV report counts and background FAERS reporting volume in the study-defined reporting-market set, 2022 Q1–2025 Q2.

Bars show quarterly counts of unique CAB/RPV reports using the left axis. The line shows total FAERS reporting volume in the study-defined reporting-market set using the right axis. These data describe reporting context only and were not used as exposure denominators, measures of treatment uptake, incidence rates, or event rates.

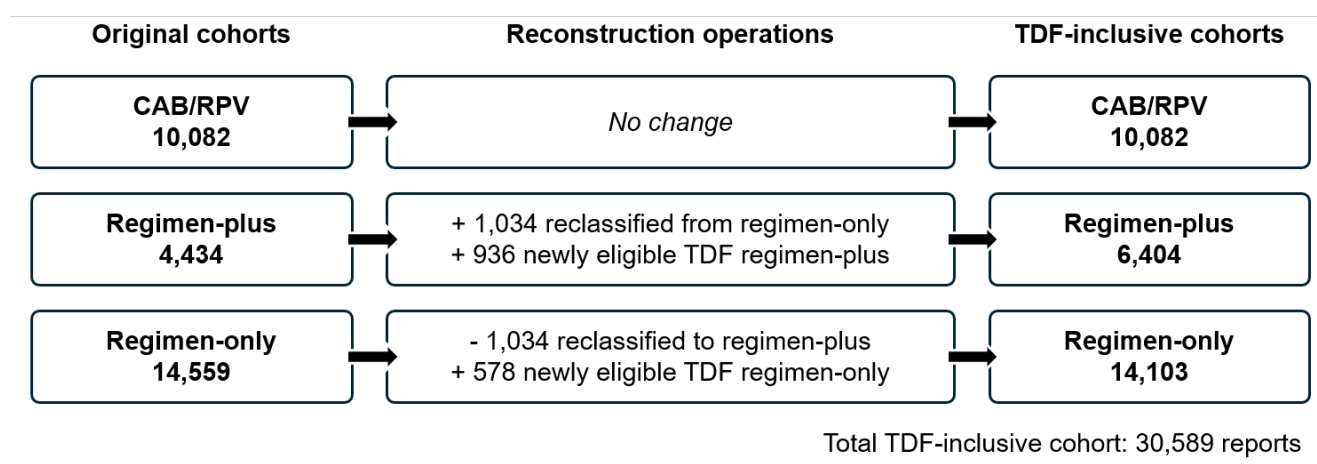
Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; FAERS, U.S. Food and Drug Administration Adverse Event Reporting System; Q, calendar quarter.



Supplementary Figure S5. Propensity-score distributions for CAB/RPV versus regimen-plus in the 3-point MACE-related reporting analyses.

Unweighted propensity-score distributions are shown for CAB/RPV and regimen-plus in the Original, complete-case, HCP-only, and US-only 3-point MACE-related analyses. The distributions are presented as a descriptive assessment of overlap; visual overlap does not establish clinical exchangeability. Quantitative SMD, ESS, and weight diagnostics are reported in Supplementary Tables S7–S10.

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; ESS, effective sample size; HCP, healthcare professional; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; PS, propensity score; SMD, standardized mean difference; US, United States.



Supplementary Figure S6. Reconstruction and reclassification of the TDF-inclusive report-level cohorts.

The TDF-inclusive comparator definitions were reapplied to all eligible reports. The cohort was reconstructed rather than created by simply appending newly eligible TDF reports. Reclassification of 1,034 existing regimen-only reports as regimen-plus explains why the regimen-only count decreased despite addition of 578 newly eligible TDF regimen-only reports.

Report-level stratum definitions: regimen-only, reports containing a complete index oral antiretroviral regimen listing without additional antiretroviral entries; regimen-plus, reports containing a complete index oral antiretroviral regimen listing together with additional antiretroviral entries.

Abbreviations: CAB/RPV, long-acting cabotegravir/rilpivirine; TDF, tenofovir disoproxil fumarate.