CARDIOVASCULAR OUTCOMES ASSOCIATED WITH INTEGRASE STRAND TRANSFER INHIBITOR–BASED ANTIRETROVIRAL THERAPY IN PEOPLE LIVING WITH HIV: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: Integrase strand transfer inhibitors (INSTIs) are the cornerstone of modern antiretroviral therapy (ART). However, emerging concerns regarding INSTI-associated weight gain and metabolic dysregulation necessitate a robust evaluation of their cardiovascular safety. This systematic review and meta-analysis synthesized evidence on the association between INSTI-based regimens and incident cardiovascular disease (CVD) among people living with HIV (PLWH). **Methods**: Following PRISMA 2020 guidelines, we searched major databases for observational cohort studies comparing INSTI-based therapy with non-INSTI regimens. Quantitative synthesis was performed using a random-effects model to estimate pooled hazard ratios (HRs) and 95% confidence intervals (CIs). **Results**: Five large-scale multinational cohort studies (2020–2023) were included. The pooled analysis demonstrated that INSTI-based therapy was not significantly associated with an elevated risk of incident CVD compared to non-INSTI regimens (HR: 1.14; 95% CI: 0.75–1.73). Individual study estimates varied, and substantial heterogeneity was observed across studies. Substantial statistical heterogeneity was observed driven by divergent study-specific estimates ranging from protective associations to modest risk increases. Individual cohorts suggested that demographic factors and baseline metabolic profiles may modulate cardiovascular outcomes. **Conclusion**: Current evidence indicates a neutral overall association between INSTI exposure and cardiovascular events in the medium term, providing clinical reassurance for their continued use as first-line therapy. However, the high inter-study heterogeneity underscores the complexity of HIV-associated cardiometabolic risk. Future longitudinal research with extended follow-up is imperative to determine whether INSTI-induced metabolic shifts translate into clinically significant cardiovascular morbidity over time.

***Keywords**: HIV; integrase strand transfer inhibitors; cardiovascular disease; antiretroviral therapy; meta-analysis.*

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INTRODUCTION

Human Immunodeficiency Virus (HIV) infection remains an enduring threat to global wellbeing, affecting millions of individuals worldwide and continuing to pose substantial challenges for healthcare systems (1). The global expansion of potent antiretroviral therapy (ART) over the past two decades has fundamentally redefined the longevity of people living with HIV (PLWH), facilitating a profound extension in life expectancy (2–4). Consequently, the clinical focus has pivoted from managing acute opportunistic infection towards addressing a growing burden of AIDS-related chronic comorbidities (5). Among these non–AIDS-related conditions, cardiovascular disease (CVD) has emerged as one of the leading contributors to morbidity and mortality in PLWH (6–8). Evidence from large scale longitudinal cohorts confirms that PLWH face a markedly elevated risk of myocardial infarction and cerebrovascular events compared with HIV-negative individuals of similar age and demographic characteristics (9–11).

The elevated cardiovascular risk observed in PLWH is multifactorial and involves a complex interplay of viral, host, and treatment-related factors (10). Chronic immune activation and systemic inflammation associated with persistent HIV infection are considered key drivers of accelerated atherosclerosis (12). Even in individuals with virologically suppressed disease, inflammatory pathways remain activated, contributing to endothelial dysfunction (13), vascular injury, and plaque formation (4,14,15). In addition, immune dysregulation and persistent cytokine production may

promote metabolic abnormalities that further increase cardiovascular risk. These underlying biological pathways are widely implicated in the accelerated progression of atherosclerotic cardiovascular complications observed in this cohort, effectively shifting the clinical burden to a significantly younger demographic compared to the general population (8,16).

Beyond the direct effects of HIV infection, traditional cardiovascular risk factors are also highly prevalent among individuals living with HIV (8,17). Smoking rates, for example, are significantly higher among PLWH than in the general population, while conditions such as hypertension, diabetes mellitus, dyslipidemia, and obesity frequently coexist in this group (10). These conventional risk factors interact with HIV-specific mechanisms to create a cumulative cardiovascular risk profile that is substantially greater than would be expected from traditional risk factors alone (18). In addition, HIV infection may alter lipid metabolism and glucose homeostasis, further contributing to the development of cardiometabolic disorders. Together, these mechanisms underscore the importance of evaluating cardiovascular outcomes when assessing the long-term safety of antiretroviral therapy (19,20).

While the advent of combination antiretroviral therapy (cART) has fundamentally redefined HIV management and markedly extended patient longevity (21). Nonetheless, this clinical success is partially shadowed by the metabolic legacy of earlier drug regimens, which continue to raise significant concerns regarding long-term cardiovascular safety. Specifically, certain classes of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been demonstrably linked to a constellation of metabolic disturbances, including atherogenic dyslipidemia, impaired insulin sensitivity, and lipodystrophy (22). These iatrogenic effects are thought to act synergistically, exacerbating the cumulative risk of atherosclerotic cardiovascular disease within this aging population (10). As treatment strategies have evolved, newer classes of antiretroviral agents have been developed with improved efficacy and safety profiles. Among these, integrase strand transfer inhibitors (INSTIs) have rapidly become a cornerstone of modern HIV therapy due to their potent antiviral activity, favorable tolerability, and relatively low potential for drug–drug interactions (23,24).

Integrase strand transfer inhibitors (INSTIs), encompassing agents such as dolutegravir, bictegravir, elvitegravir, and raltegravir have emerged as the cornerstone of first-line antiretroviral therapy within contemporary international guidelines (25). These compounds specifically disrupt the integration of proviral DNA into the host genome, thereby halting a pivotal phase of the HIV replication cycle (26). Due to their superior virologic potency and refined safety profiles relative to predecessor drug classes, INSTI-based regimens are now ubiquitously deployed across both treatment-naive and treatment-experienced populations (27). Rigorous clinical evaluations have consistently underscored the capacity of INSTIs to induce rapid viral suppression and sustain long-term therapeutic efficacy, solidifying their status as a preferred modality for initiating treatment (24,28).

Despite their clinical advantages, emerging evidence has raised questions regarding the potential cardiometabolic effects of INSTI-based therapy (24). Several observational studies and clinical analyses have reported that INSTI exposure may be associated with significant weight gain and changes in body composition, particularly among treatment-naïve individuals initiating therapy (29–31). This phenomenon has been observed across multiple cohorts and may be more pronounced in certain populations, including women and individuals of African descent. Weight gain and metabolic changes associated with INSTI therapy have raised concerns that these agents could indirectly influence cardiovascular risk through the development of obesity, insulin resistance, or dyslipidemia (21,32,33).

In addition to weight gain, INSTI-based regimens have also been linked to metabolic disturbances that could potentially influence cardiovascular outcomes. Some studies have reported increases in body mass index, alterations in lipid profiles, and changes in glucose metabolism following initiation of INSTI therapy (21,34,35). While these metabolic effects are not universally observed and their clinical significance remains uncertain, they have prompted ongoing investigation into the long-term cardiometabolic safety of INSTIs. Importantly, the relationship between metabolic changes and actual cardiovascular events is complex, and metabolic risk factors do not always translate directly into increased rates of clinical cardiovascular disease (29,36).

Recent large-scale cohort studies have attempted to directly examine the relationship between INSTI exposure and cardiovascular outcomes among PLWH. These studies have produced heterogeneous findings, with some suggesting an increased risk of cardiovascular events associated with INSTI use, while others have reported neutral or even protective associations. Differences in study design, cohort characteristics, duration of follow-up, and analytical methods may contribute to these conflicting results (22,30,31,37,38). Furthermore, observational studies evaluating antiretroviral therapy are often subject to confounding by indication and treatment selection

bias, which can complicate the interpretation of their findings. Consequently, the current evidence base remains inconclusive regarding whether INSTI-based therapy meaningfully alters cardiovascular risk in PLWH (39).

Given the widespread global adoption of INSTI-based regimens as the preferred first-line treatment for HIV infection, clarifying their potential association with cardiovascular disease is of considerable clinical importance. Understanding whether these therapies influence cardiovascular outcomes has important implications for long-term patient management, particularly as the population of PLWH continues to age and accumulate traditional cardiovascular risk factors. A systematic synthesis of the available evidence may provide a more precise estimate of cardiovascular risk associated with INSTI exposure and help reconcile the inconsistencies observed across individual studies. Therefore, the present study aimed to conduct a systematic review and meta-analysis to evaluate the association between integrase strand transfer inhibitor–based antiretroviral therapy and the risk of incident cardiovascular disease in people living with HIV.

METHODS

Study Design and Reporting Guidelines

To elucidate the impact of INSTI-based therapy on incident cardiovascular disease, a comprehensive systematic review and meta-analysis was executed. The research methodology followed a structured approach to evidence synthesis, with all reporting procedures meticulously aligned with the PRISMA guidelines to ensure scholarly transparency and methodological integrity.

Search Strategy and Data Sources

A systematic literature search was executed across PubMed, Cochrane Library, and ScienceDirect to identify a broad range of biomedical and clinical epidemiological studies relevant to HIV treatment and cardiovascular outcomes. The search strategy combined terms related to HIV infection, integrase strand transfer inhibitors, and cardiovascular disease.

The keywords used in the search strategy included combinations of the following terms: “HIV”, “human immunodeficiency virus”, “integrase inhibitor”, “integrase strand transfer inhibitor”, “INSTI”, “dolutegravir”, “bictegravir”, “elvitegravir”, “raltegravir”, “cardiovascular disease”, “cardiovascular events”, “myocardial infarction”, and “stroke.” Boolean operators were applied to combine these terms appropriately for each database. This expansive approach was designed to capture all relevant observational data regarding INSTI-associated cardiovascular risks. To ensure study retrieval was exhaustive, we manually scrutinized the bibliographies of all included articles and relevant reviews to identify additional eligible reports not captured during the primary database interrogation.

Eligibility Criteria

Studies were considered based on the PICO (Population, Intervention, Comparison, and Outcome) framework. Eligible studies included adults living with HIV receiving antiretroviral therapy. The intervention focused on INSTI-based regimens (dolutegravir, bictegravir, elvitegravir, or raltegravir), while the comparator group consisted of individuals on non-INSTI regimens, such as protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The primary outcome of interest was incident cardiovascular disease, defined as clinically diagnosed cardiovascular events such as myocardial infarction, stroke, or other major cardiovascular complications reported during follow-up. Studies were eligible if they reported adjusted or unadjusted hazard ratios with corresponding confidence intervals, or if sufficient data were available to calculate effect estimates for inclusion in the meta-analysis.

Eligible study designs included observational cohort studies, including retrospective cohort analyses, prospective cohort studies, and target trial emulation studies derived from large clinical databases or HIV cohort collaborations. Exclusion criteria comprised review articles, case reports, editorials, conference abstracts lacking full data, pediatric studies, and animal models. Studies without a clear comparator group or defined cardiovascular endpoints were also excluded.

Study Selection Process

The selection of studies was executed in accordance with PRISMA 2020 protocols. All records identified from the database searches were first screened by reviewing titles and abstracts to assess their relevance to the research question. Articles that clearly deviated from the inclusion criteria were excluded at this stage.

Potentially eligible reports were subsequently subjected to a rigorous full-text review to confirm adherence to our predefined PICO criteria. Specifically, we scrutinized the study population, INSTI-based exposure, the presence of non-INSTI comparators (PIs or NNRTIs), and the clinical definition of cardiovascular outcomes. Only studies providing robust quantitative data and satisfying all eligibility requirements were progressed to the final qualitative synthesis and meta-analysis.

Data Extraction

Data extraction was performed using a predefined standardized extraction form to ensure consistency across studies. The extracted information included study characteristics, participant demographics, treatment exposure, comparator groups, outcome definitions, follow-up duration, and effect estimates for cardiovascular events. Additional information regarding statistical adjustment methods and potential confounding variables was also collected when available.

For each study, the primary effect measure extracted for meta-analysis was the hazard ratio for incident cardiovascular events associated with INSTI-based therapy compared with non-INSTI regimens. When studies reported multiple models, the most fully adjusted hazard ratio was preferentially extracted to minimize confounding. Extracted data were subsequently organized into a structured dataset suitable for quantitative synthesis.

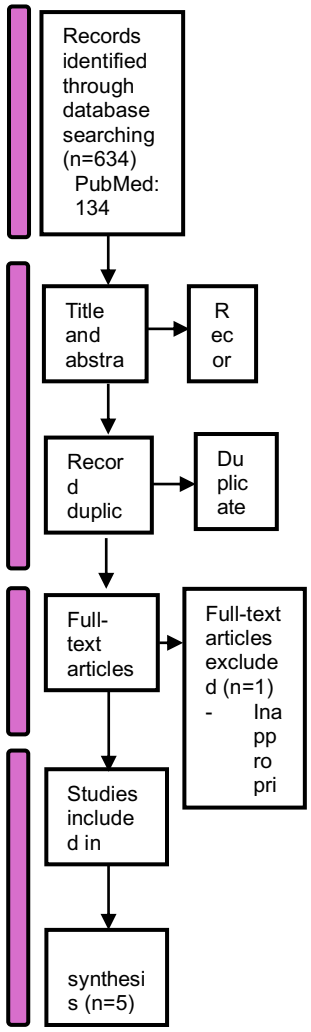


Figure 1. Diagram flow of literature search strategy for this meta-analysis

Risk of Bias Assessment

The methodological quality of the included observational studies was rigorously evaluated across four key domains: participant selection, cohort comparability, outcome measurement, and adjustment for confounding variables. While residual confounding is inherently present in large-scale clinical datasets, we critically assessed the robust multivariable models and propensity-score matching (PSM) techniques employed by the authors to mitigate these effects. Overall, the evidence was characterized by a moderate risk of bias, a classification consistent with the observational nature of the included cohorts. This assessment underscores the necessity for cautious interpretation of the synthesized effect estimates while acknowledging the high ecological validity of the data sources

Statistical Analysis

Quantitative synthesis was performed to determine the association between INSTI-based therapy and incident cardiovascular disease. The pooled effect size was calculated using hazard ratios (HRs) with corresponding 95% confidence intervals reported in the individual studies. Given the anticipated clinical and methodological diversity among the observational cohorts, a random-effects model was prioritized over a fixed-effects approach to provide a more conservative and generalizable estimate.

Statistical heterogeneity was quantified using the Chi-square test and the I^2 statistic, where an I^2 greater than 50% denoted substantial inconsistency across studies. The overall summary effect and the weight of individual studies were visualized through forest plots. All analyses were executed using Review Manager (RevMan) version 5.4, with statistical significance set as a two-sided $p < 0.05$.

First Author (Year)	Country / Data Source	Study Design	Population Characteristics	Sample Size (INSTI / Non-INSTI)	Mean Age (years)	% Female	INSTI
Rebeiro et al. (2023)	United States – IBM MarketScan Commercial, Medicare Supplemental, and Medicaid claims databases	Retrospective cohort	Treatment-naïve adults (≥18 yrs) living with HIV initiating ART after Aug 2013	7059 / 7017 (weighted cohorts)	38.6 vs 39.0	23.2% vs 23.9%	Elvite Dolut Bicteg Ralteg
O'Halloran et al. (2020)	United States – IBM MarketScan Commercial and Multi-State Medicaid databases	Retrospective cohort	Adults living with HIV initiating ART between 2008–2015	5069 / 15204	NR	NR	Integra inhibit (dolut elviteg
Surial et al. (2023)	Switzerland – Swiss HIV Cohort Study	Prospective cohort	ART-naïve adults with HIV initiating first-line ART between May 2008 and May 2021	1837 / 3525	Median 38 years	21%	INSTI (dolut elviteg
Neesgaard et al. (2022)	Multinational (Europe & Australia) – RESPOND cohort consortium	Prospective multicentre cohort	Adults (≥18 years) living with HIV receiving ART with no INSTI exposure before baseline	14000 exposed during follow-up / 29340 total cohort	Median 44.3 years	25.50%	INSTI (dolut elviteg
Rein et al. (2023)	Multinational (Europe & North America) – HIV-CAUSAL Collaboration + ART Cohort Collaboration	Target trial emulation using pooled observational cohorts	Adults ≥18 years living with HIV initiating ART (ART-naïve) or switching ART (ART-experienced) without prior cardiovascular event	ART-naïve: 10,767 / 8,292; ART-experienced: 7,875 / 67,411	ART-naïve median 39 years; ART-experienced median 50 years	~12–15% female	INSTI (dolut elviteg combi

Table 1. Characteristics and resuls of the included studies

RESULTS

Study Selection

The initial multi-database search across PubMed (n = 134), Cochrane Library (n = 80), and ScienceDirect (n = 420) yielded a total of 634 potentially relevant records. After consolidating these results into a unified library, we performed a rigorous title and abstract screening based on our predefined eligibility criteria. At this preliminary stage, 627 records were excluded due to a lack of relevance to cardiovascular outcomes, non-comparative study designs, or focus on pediatric populations. Other reasons for exclusion included mechanistic studies without clinical endpoints, case reports, editorials, and conference abstracts lacking extractable data.

Following the title and abstract screening, seven potentially eligible studies were retained for further assessment. Duplicate screening was subsequently performed to ensure that overlapping reports from the same cohort or repeated publications were not included in the final analysis. During this step, one duplicate record was identified and removed, leaving six unique studies for detailed full-text review.

The full-text eligibility assessment was conducted to confirm that each study fulfilled all components of the predefined PICO framework, including the appropriate study population, exposure and comparator groups, and the reporting of cardiovascular outcomes that could be quantitatively synthesized. Each article was carefully evaluated to ensure that the cardiovascular outcomes were clearly defined and that the statistical effect estimates were extractable for meta-analysis. During this stage, one study was excluded because it did not meet the inclusion criteria, primarily due to an inappropriate study population and the absence of extractable outcome measures relevant to the comparison of INSTI-based therapy versus non-INSTI regimens.

Following a rigorous eligibility assessment, five studies met all inclusion criteria and were progressed to the qualitative synthesis. Notably, each of these five studies provided comprehensive quantitative data—specifically hazard ratios (HRs) and 95% confidence intervals (CIs)—facilitating their integration into the formal meta-analysis. Consequently, all five identified reports were utilized for both qualitative and quantitative evidence synthesis. The systematic trajectory of study identification, screening, and final inclusion is detailed in Figure 1, in strict accordance with the PRISMA 2020 framework.

Characteristics of Included Studies

The final meta-analysis comprised five observational cohort studies evaluating the correlation between INSTI-based antiretroviral therapy and cardiovascular risk among people living with HIV (PLWH). Published between 2020 and 2023, these reports utilized high-fidelity, large-scale databases from North America and Europe. By leveraging expansive clinical registries and multinational collaborations, the included studies provided robust longitudinal data across diverse HIV-positive populations, ensuring high external validity for the synthesized cardiovascular outcomes.

The included studies comprised Jane A. O'Halloran et al. (2020), Nina Neesgaard et al. (2022), Stephen R. Rebeiro et al. (2023), Sophia M. Rein et al. (2023), and Andri Rauch / Surial et al. (2023). Collectively, these studies represented a large number of individuals living with HIV who initiated or switched antiretroviral therapy during routine clinical care. Most studies utilized retrospective cohort designs based on clinical registries, administrative databases, or multinational HIV cohort collaborations. The availability of these large datasets allowed for robust statistical analyses and adjustment for multiple confounding variables.

Across the included studies, the exposure of interest was treatment with INSTI-based antiretroviral regimens, which typically included agents such as dolutegravir, bictegravir, elvitegravir, or raltegravir in combination with nucleoside reverse transcriptase inhibitors. These regimens represent the current cornerstone of first-line antiretroviral therapy in many international HIV treatment guidelines due to their high virologic efficacy and favorable tolerability profile. The comparison group consisted of individuals receiving non-INSTI–based antiretroviral regimens, most commonly regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs).

The primary outcome assessed across the included studies was incident cardiovascular disease, typically defined as a composite endpoint encompassing myocardial infarction, stroke, or other major cardiovascular events or procedures. Although the exact definitions varied slightly among studies, the outcome measures consistently reflected clinically meaningful cardiovascular complications. Follow-up durations varied among studies but generally ranged from approximately 1.5 to 5 years, allowing sufficient time to capture incident cardiovascular events following initiation of antiretroviral therapy.

Most studies incorporated multivariable adjustment or propensity-based methods to control for potential confounding factors. These adjustments commonly included demographic variables such as age and sex, HIV-specific clinical indicators including CD4 cell count and viral load, as well as traditional

cardiovascular risk factors such as hypertension, diabetes mellitus, smoking status, dyslipidemia, and body mass index. The use of these adjustment strategies aimed to reduce confounding by indication and better isolate the potential effect of INSTI exposure on cardiovascular risk.

Overall, the methodological quality of the included studies was considered acceptable for observational evidence synthesis. Although observational cohort designs inherently carry risks of residual confounding, the included studies employed large datasets, rigorous statistical adjustments, and clearly defined cardiovascular endpoints. Based on the predefined methodological assessment framework, the risk of bias across the included studies was categorized as moderate, consistent with high-quality observational cohort evidence.

Meta-analysis of Incident Cardiovascular Events

Figure 2. Pooled results for incident of cardiovascular events

A meta-analysis was executed to quantitatively synthesize the available evidence regarding the association between INSTI-based antiretroviral therapy and the risk of incident cardiovascular disease among PLWH. Data from five cohort studies were pooled, focusing on reported hazard ratios comparing INSTI-based regimens against non-INSTI alternatives. To address anticipated clinical and methodological diversity, a random-effects model was employed, providing a robust estimate of the collective cardiovascular risk across the identified study populations.

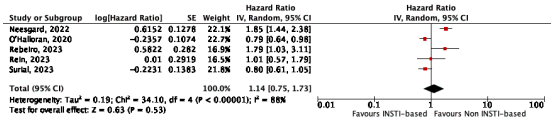
The pooled analysis revealed that INSTI-based therapy was not significantly associated with an increased risk of cardiovascular events compared to non-INSTI regimens. The combined hazard ratio for incident CVD was 1.14 (95% CI: 0.75–1.73). As the confidence interval crossed the null value (1.0), the aggregate estimate indicates no statistically significant increase or reduction in cardiovascular risk among PLWH.

Despite the non-significant pooled effect, individual study estimates exhibited substantial variability. For instance, Neesgaard et al. (2022) reported a significantly higher risk associated with INSTI exposure (HR: 1.85; 95% CI: 1.44–2.38). Conversely, O'Halloran et al. (2020) observed a modest but statistically significant protective association (HR: 0.79; 95% CI: 0.64–0.98).

Variable cardiovascular risk estimates were further observed in recent cohorts Rebeiro et al. (2023) reported a modest but significant risk increase (HR: 1.79; 95% CI: 1.03–3.11), whereas Rein et al. (2023) found an effect size nearly at the null (HR: 1.01; 95% CI: 0.57–1.79). Conversely, Surial et al. (2023) observed a hazard ratio below unity (HR: 0.80; 95% CI: 0.61–1.05), suggesting a potential but non-significant reduction in cardiovascular event.

This marked divergence was reflected in substantial statistical heterogeneity $I^2 = 88\%$; $\chi^2 = 34.10$, $p < 0.00001$), indicating that the inter-study variability is unlikely to be attributable to chance. Such significant heterogeneity may stem from disparities in baseline cardiovascular risk profiles, variations in antiretroviral therapy (ART) history, and diverse methodologies for confounding adjustment across the multinational cohorts.

Nevertheless, when the evidence from all five studies was synthesized, the overall pooled estimate indicated no statistically significant association between INSTI-based antiretroviral therapy and the incidence of cardiovascular disease among people living with HIV. The forest plot illustrating the



individual study estimates and the pooled effect size is presented in Figure 2, providing a visual representation of the distribution of study results and the overall summary effect.

DISCUSSION

Principal Findings

This systematic review and meta-analysis synthesized longitudinal evidence from five large-scale multinational cohorts to evaluate the cardiovascular safety of INSTI-based antiretroviral therapy. Our pooled analysis indicates a neutral association between INSTI exposure and incident cardiovascular disease (CVD) compared to non-INSTI regimens. While certain individual cohorts suggested elevated risks, the aggregate evidence suggests that INSTIs now the cornerstone of modern HIV management due to their superior efficacy and resistance barriers, do not substantially augment cardiovascular morbidity in PLWH (24).

These results provide essential clinical reassurance as INSTIs continue to be prioritized in international treatment guidelines. However, the substantial inter-study heterogeneity observed underscores the multifaceted nature of CVD in the context of HIV. The divergence in findings between cohorts suggests that the cardiovascular impact of ART is likely modulated by a complex interplay of systemic inflammation, metabolic shifts, and traditional risk profiles. Consequently, our findings

advocate for a nuanced interpretation of ART-associated risks, emphasizing that cardiovascular monitoring remains imperative despite the overall neutral safety signal observed in this synthesis.

Pathophysiological Considerations

The elevated cardiovascular risk observed in people living with HIV (PLWH) is driven by a multifaceted, synergistic interplay of virus-specific, host-related, and treatment-associated mechanisms. Chronic immune activation and persistent systemic inflammation serve as the primary biological conduits linking HIV infection to accelerated atherosclerosis. Notably, even in individuals achieving sustained virological suppression, low-grade immune activation remains a persistent challenge, contributing significantly to endothelial dysfunction, vascular inflammation, and coronary plaque instability (10,11,16). These underlying pathological processes facilitate the premature onset of atherosclerotic cardiovascular disease (ASCVD), potentially elucidating why cardiovascular events occur more frequently and at chronologically younger ages in PLWH compared to HIV-negative populations (40).

Inflammatory pathways triggered during chronic HIV infection involve upregulated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other soluble mediators that directly exacerbate vascular injury. This persistent state of immune activation further catalyzes oxidative stress and profound alterations in lipid metabolism, both of which serve as critical drivers of atherosclerotic progression (16). Recent evidence suggests that these HIV-specific inflammatory mechanisms likely exert a dominant influence on long-term cardiovascular risk, potentially overshadowing the direct metabolic impacts of specific antiretroviral drug classes (41).

Beyond HIV-mediated inflammation, traditional cardiovascular risk factors are disproportionately prevalent among PLWH and contribute substantially to the cumulative burden of cardiovascular disease in this population. Smoking prevalence remains significantly higher among PLWH than in the general population, while metabolic comorbidities—including hypertension, dyslipidemia, obesity, and diabetes mellitus—are frequently observed clinical feature (19,20). These conventional risk factors interact dynamically with HIV-related inflammatory pathways, generating a cumulative cardiometabolic risk profile that is considerably greater than what would be predicted by traditional risk models alone (42,43). Consequently, cardiovascular outcomes in PLWH are determined by a sophisticated, multi-layered interplay of biological, clinical, and behavioral determinants (44).

Metabolic Effects of INSTI-Based Therapy

One of the primary concerns regarding INSTI therapy relates to its potential metabolic and weight-related effects, which have been reported in several clinical and observational studies. Weight gain following initiation of INSTI-based regimens has been consistently observed in multiple cohorts, particularly among treatment-naïve individuals starting therapy (21). The magnitude of weight gain appears to vary across populations and may be influenced by factors such as sex, ethnicity, baseline body mass index, and the specific antiretroviral regimen used (45,46).

Several physiological mechanisms have been hypothesized to mediate this association. Beyond the "return-to-health" phenomenon—where rapid viral suppression leads to weight gain as a markers of clinical recovery, recent research suggests direct drug-induced effects. These include the inhibition of adipocyte differentiation, mitochondrial dysfunction in adipose tissue, and potential interference with melanocortin-4 receptor (MC4R) pathways involved in central appetite regulation (21,44).

Despite these metabolic shifts, the direct translation of INSTI-associated weight gain into incident cardiovascular events remains characterized by a significant "lag time." While obesity and metabolic syndrome are established drivers of cardiovascular risk, the transition from adiposity to clinically manifest myocardial infarction or stroke typically requires prolonged observation. The follow-up durations in the studies included in this meta-analysis generally spanning 3 to 5 years, may be insufficient to capture the full trajectory of cardiometabolic risk associated with INSTI-induced weight changes (47,48). Consequently, the neutral association observed in our pooled analysis might reflect a "latency period" in the evolution of cardiovascular outcomes, necessitating long-term surveillance to accurately assess the late-stage risks of these metabolic perturbations.

Comparison With Previous Studies

The findings of the present meta-analysis are broadly consistent with several previous investigations evaluating cardiovascular outcomes among individuals receiving contemporary antiretroviral therapy. Large cohort studies have produced heterogeneous results, reflecting differences in study design, population characteristics, and analytical approaches (30,39).

Some observational studies have suggested that INSTI exposure may be associated with increased cardiovascular risk in specific patient populations, particularly among individuals with pre-existing cardiometabolic risk factors (49). However, other analyses have reported neutral associations between

INSTI therapy and cardiovascular events, indicating that INSTI-based regimens may not independently drive cardiovascular disease risk (39). These discrepancies highlight the importance of considering confounding factors such as baseline cardiovascular risk, treatment history, and comorbid conditions when interpreting observational data.

Moreover, emerging epidemiological evidence suggests that traditional cardiovascular risk factors may exert a greater influence on cardiovascular outcomes than the specific class of antiretroviral therapy used (49). Factors such as smoking, hypertension, dyslipidemia, and diabetes appear to remain the strongest predictors of cardiovascular disease in PLWH, reinforcing the importance of comprehensive cardiovascular risk management in this population. In this context, INSTI-based therapy may represent only one component of a broader cardiometabolic risk profile.

Clinical Implications

The clinical implications of these findings are particularly salient given the global transition toward INSTI-dominant antiretroviral therapy (ART). Current international guidelines prioritize INSTIs as the preferred first-line therapy, citing their superior virologic suppression, higher genetic barrier to resistance, and favorable tolerability profiles (23,24). The absence of a definitive association between INSTI exposure and incident cardiovascular events in this meta-analysis provides critical clinical reassurance regarding the cardiovascular safety of these regimens in routine practice.

However, these results should not lead to clinical complacency. Despite the lack of a drug-specific cardiovascular signal, PLWH inherently possess an elevated risk of ASCVD due to the synergistic effects of chronic immune activation and a high burden of conventional risk factors (50,51). Therefore, clinicians must maintain a comprehensive and proactive approach to cardiovascular risk stratification. Integrating regular cardiovascular screenings, targeted lifestyle interventions, and aggressive smoking cessation counseling remains a cornerstone of long-term HIV care (52,53).

Furthermore, monitoring metabolic changes associated with INSTI therapy, such as weight gain or alterations in lipid and glucose metabolism, remains important. Early identification of cardiometabolic abnormalities may allow timely intervention and help reduce the long-term burden of cardiovascular disease among PLWH receiving antiretroviral therapy (54,55).

Limitations

Several limitations warrant consideration when interpreting these findings. First, the inclusion of observational cohort studies introduces inherent susceptibility to selection bias and residual confounding. While most primary studies employed robust multivariable adjustment or propensity-score matching (PSM) to mitigate these effects, the influence of unmeasured confounders cannot be entirely excluded (42).

Second, the presence of substantial statistical heterogeneity (I^2 = 88%) reflects diverse cohort demographics, varying follow-up durations, and inconsistent definitions of cardiovascular outcomes across the multinational registries. This variability necessitates a cautious interpretation of the aggregate effect estimates regarding their broader generalizability.

Third, many studies utilized composite cardiovascular endpoints, which may obscure potential differences in specific events, such as myocardial infarction or stroke, compared to heart failure or peripheral vascular disease. Future research focusing on granular, individual endpoints is required to refine the cardiovascular safety profile of INSTI therapy (56).

Finally, the follow-up periods in several cohorts were relatively modest in comparison to the protracted natural history of atherosclerotic disease. Given the metabolic changes associated with INSTI use, longitudinal studies with extended observation windows are essential to determine whether these early adiposity-related shifts translate into clinically significant cardiovascular morbidity over time (57).

Future Research Directions

Future investigations should prioritize long-term longitudinal studies with extended follow-up durations to definitively establish the cardiovascular safety profile of INSTI-based regimens. While observational data provide real-world insights, randomized controlled trials (RCTs) specifically powered to evaluate cardiometabolic endpoints are essential to provide robust causal evidence and mitigate the limitations of residual confounding inherent in cohort analyses.

Furthermore, future research should explore potential subgroup differences in cardiovascular risk, including variations based on age, sex, ethnicity, baseline metabolic status, and specific INSTI agents. Understanding these factors may help identify patient populations that require closer cardiometabolic monitoring when receiving INSTI therapy.

Finally, there is a critical need for implementation research focused on integrating multidisciplinary cardiovascular risk management into routine HIV care. As the global population of PLWH continues to age, developing and validating HIV-specific risk stratification tools will be imperative to optimizing long-term clinical outcomes and reducing

the disproportionate burden of ASCVD in this population.

CONCLUSION

In this systematic review and meta-analysis of large-scale observational cohorts, INSTI-based antiretroviral therapy was not significantly associated with an increased risk of incident cardiovascular disease (CVD) among people living with HIV (PLWH). Although individual studies exhibited variable risk estimates, the consolidated evidence indicates a neutral overall association between INSTI exposure and cardiovascular outcomes. These findings provide critical clinical evidence supporting the cardiovascular safety profile of INSTI-based regimens, which currently serve as the cornerstone of first-line therapy in international HIV treatment guidelines

Nevertheless, the cardiovascular health of PLWH is governed by a multifaceted interplay of chronic immune activation, metabolic dysregulation, and traditional risk factors. Consequently, a comprehensive and proactive approach to cardiovascular risk assessment remains an indispensable component of longitudinal HIV care. To fully elucidate the long-term cardiometabolic trajectory of modern ART, future large-scale longitudinal studies with extended follow-up are warranted. Such research should focus on identifying high-risk patient subgroups to ensure optimized, person-centered cardiovascular monitoring and prevention strategies in the aging HIV population.

Nevertheless, the cardiovascular health of people living with HIV remains influenced by a complex interplay of chronic inflammation, metabolic changes, and traditional cardiovascular risk factors. Therefore, comprehensive cardiovascular risk assessment and management remain essential components of long-term HIV care. Future large-scale longitudinal studies with extended follow-up are needed to further clarify the long-term cardiometabolic effects of INSTI-based therapy and to identify patient subgroups that may require closer cardiovascular monitoring.

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