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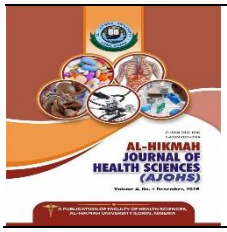

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Review Article

Efavirenz-based Treatment Effects on CD4+ Cell Count Changes in People Living with HIV/AIDS: Assessing Heterogeneity and Publication Bias

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ABSTRACT

Background: Efavirenz (EFV)–based regimens have long been integral to antiretroviral therapy (ART). The extent to which EFV contributes to immunologic recovery remains clinically relevant, where EFV is still prescribed.

Objective: To quantify CD4+ T-cell count change associated with EFV-based treatment and to assess heterogeneity and publication bias.

Methods: We systematically searched PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar from 2000 to Aug 31, 2025, screened per PRISMA 2020, and included randomized or observational studies reporting baseline and follow-up CD4+ counts (or change/SD) for EFV-based arms. Random-effects meta-analysis summarized mean change; heterogeneity (Q, I^2), leave-one-out sensitivity, and funnel plots/Egger's test evaluated robustness and bias.

Results: Five studies met criteria. The pooled mean CD4+ increase with EFV-based therapy was 184.5 cells/μL (95% CI 65.1–303.9), with $I^2 = 0\%$. Sensitivity analyses did not materially alter estimates. Funnel-plot visual inspection showed no clear asymmetry, though power was limited (n = 5).

Conclusions: EFV-based ART is associated with a clinically meaningful rise in CD4+ count—exceeding typical first-year gains observed after ART initiation—though precision is limited by the small evidence base. Findings should be interpreted alongside contemporary guidelines that prefer INSTI-based first-line regimens; nonetheless, results inform settings where EFV remains in use or is clinically indicated.

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Introduction

Human Immunodeficiency Virus (HIV) infection remains a global health challenge, with millions of individuals worldwide relying on antiretroviral therapy (ART) for the management of their condition (Goga *et al*., 2020). Efavirenz, a non-nucleoside

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reverse transcriptase inhibitor, has been a cornerstone of ART regimens due to its efficacy and accessibility (WHO, 2017). It plays a vital role in suppressing viral replication, reducing morbidity and mortality, and improving the quality of life for people living with HIV (Papot *et al*., 2021). However, the impact of Efavirenz on CD4+ cell count change, a critical marker of immune system health in HIV patients, has been a subject of ongoing investigation and debate (Gallant *et al.,* 2006; UNAIDS, 2016). While individual studies have reported varying effects (Lennox *et al*., 2009, Cohen *et al*., 2011, Sax *et al*., 2012, Walmsley *et al*., 2013), often with substantial differences in sample sizes and characteristics, a comprehensive understanding of Efavirenz's influence on CD4+ cell counts necessitates a systematic meta-analysis.

This meta-analysis seeks to synthesize existing evidence from multiple studies to provide a robust assessment of Efavirenz's treatment effects on CD4+ cell count change. By quantifying these effects, assessing heterogeneity across studies, and evaluating the potential for publication bias, we aim to enhance our understanding of the drug's immunological impact in HIV patients. This knowledge is crucial for clinicians, researchers, and policymakers in optimizing treatment strategies and ultimately improving outcomes for individuals living with HIV.

In this context, we present a meta-analysis that rigorously examines the available data, contributing to the growing body of evidence that informs clinical decisions and advances our understanding of HIV management.

Materials and Methods

Search Strategy and Data Sources

To investigate the effects of Efavirenz (EFV)-based regimen on CD4+ cell count change in people living with HIV/AIDS, we conducted a systematic review and meta-analysis. Our comprehensive search was executed in electronic databases, including PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar, utilizing the predefined search term combinations of Medical Subject Headings (MeSH) and free-text terms such as: “Efavirenz”, “CD4+ cell count”, “HIV treatment”, “Meta-analysis”, “Efavirenz Treatment Effects”.

Study Selection Criteria

Inclusion Criteria

Randomized controlled trials (RCTs) or Observational studies that evaluated Efavirenz-based therapy in people living with HIV/AIDS, Studies that reported baseline and follow-up CD4+ cell counts in people living with HIV/AIDS on Efavirenz-based treatment, and Studies with clearly defined Efavirenz-based treatment regimens and studies that provided sufficient statistical information for the meta-analysis were all included.

Exclusion Criteria

Studies that did not report CD4+ cell count changes in people living with HIV/AIDS on Efavirenz-based treatment, Studies with incomplete or unclear methodology, non-English publications, Case reports, reviews, editorials, and conference abstracts were all excluded.

Study Selection Process

We performed a comprehensive search in PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane Library (CENTRAL), and Google Scholar from January 1, 2000, to August 31, 2025. No study-design filters were applied at the database level; design eligibility was handled during screening. Language was limited to English, humans only. Example reproducible strings were as follows: PubMed (last run Aug 31, 2025): (("HIV Infections"[Mesh] OR HIV[tiab] OR AIDS[tiab]) AND (Efavirenz[Mesh] OR efavirenz[tiab] OR EFV[tiab]) AND ("CD4 Lymphocyte Count"[Mesh] OR CD4[tiab] OR "CD4 cell"[tiab]) AND (randomized controlled trial[pt] OR cohort[tiab] OR observational[tiab] OR trial[tiab])) AND ("2000/01/01"[Date - Publication]: "2025/08/31"[Date - Publication]); Filters: Humans; English. Scopus (TITLE-ABS-KEY): (HIV OR AIDS) AND (efavirenz OR EFV) AND ("CD4" OR "CD4 cell" OR "CD4 lymphocyte count") AND (random W/2 trial OR cohort OR observ) AND PUBYEAR > 1999 AND PUBYEAR < 2026. Web of Science (TS): (HIV OR AIDS) AND (efavirenz OR EFV) AND ("CD4" OR "CD4 lymphocyte count") AND (random NEAR/2 trial OR cohort OR observ). Cochrane Library: (HIV OR AIDS):ti,ab,kw AND (efavirenz OR EFV):ti,ab,kw AND ("CD4"):ti,ab,kw. Google Scholar (screened first 200 results): efavirenz CD4 change randomized HIV "mean change". We also hand-searched reference lists of included studies.

Data Extraction

Two independent reviewers extracted the following data: Study details (author, year, country, study design), Sample size, Mean baseline and follow-up CD4+ cell counts, Efavirenz-based treatment regimens, Duration of follow-up and Statistical measures (standard deviation, confidence intervals, p-values)

Risk of Bias Assessment

The Cochrane Risk of Bias Tool was used for the randomized controlled trials. The Newcastle-Ottawa

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Scale was used for observational studies and discrepancies were resolved by a third reviewer.

Data Synthesis and Statistical Analysis

Meta-Analysis Approach

A random-effects model was used to pool effect sizes. Heterogeneity was assessed using Cochran's Q test and I^2 statistics. A leave-one-out sensitivity analysis was conducted to assess the robustness of findings.

Assessment of Publication Bias

Funnel plot was used for visual assessment and Egger's regression test was conducted to quantify potential bias.

Results

In the results section, we presented the primary outcome, which is the pooled estimate of CD4+ cell count change from baseline associated with EFV treatment, along with the corresponding 95% confidence interval (CI). Subsequently, the discussion section contextualized the results within the background, considering factors such as patient demographics, study design, and potential sources of heterogeneity. The search included peer-reviewed articles published in English from 2000 to 2024. The initial database search yielded a total of 1,244 records. After removing duplicates, we were left with about 572 unique records. We provide a transparent account of the number of records identified and screened, along with insights from the PRISMA flowchart (Figure 1), illustrating the study selection procedure.

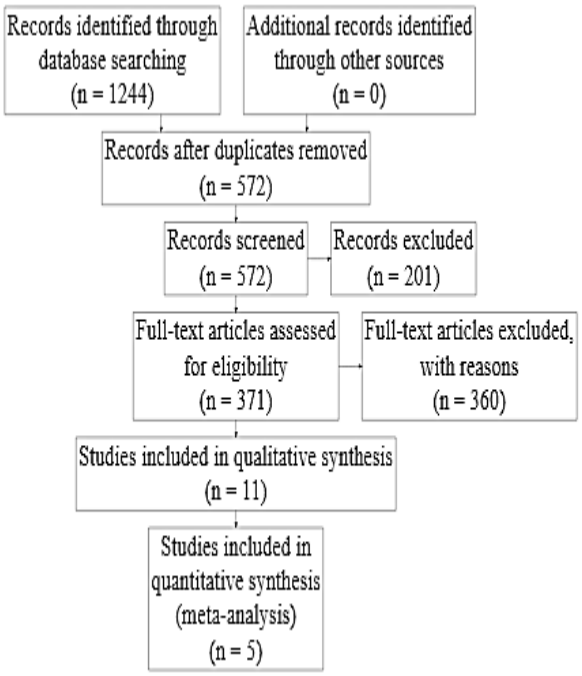

Figure 1: PRISMA guideline in study selection

Study Characteristics

A total of five studies were included in this meta-analysis, evaluating the effect of Efavirenz-based regimens on CD4+ cell count change from baseline in patients with HIV. The characteristics of these studies, including author names and publication years, are summarized in Table 1.

Table 1: Characteristics of Included Studies

Study	Treatment Arm	N	% male	Age, y	Baseline CD4+, cells/mL (SD)	Baseline viral load, log10 RNA copies/mL, (SD)	CD4+ change, cells/μL (SD)	VS HIV RNA <50 copies/mL (n/N)	AEs (n/N)
Gallant *et al*., 2006	EFV + TDF/FTC	255	85.88	38	246 (171.9)	5.03 (0.54)	190 (107.3)	196/255	-
Sax *et al*., 2012	EFV + TDF/FTC	352	89.77	38	382 (170.2)	4.78 (0.6)	206 (153.4)	296/352	334/352
Walmsley *et al*., 2013	EFV + TDF/FTC	419	84.96	35	339	4.7	208.16 (190.65)	338/419	387/419
Lennox *et al*., 2009	EFV + TDF/FTC	282	81.91%	36.9	217.4 (133.6)	5 (0.6)	163.3 (121.2)	230/281	272/282
Cohen *et al*., 2011	EFV + CHOICE	338	72.19%	36.3	263	5	171 (150.1)	276/338	312/338

EFV (Efavirenz), TDF (Tenofovir Disoproxil Fumarate), FTC (Emtricitabine) and an alternative regimen (CHOICE)

Meta-Analysis Results

The random-effects meta-analysis estimated the pooled effect size of Efavirenz-based regimens on CD4+ cell count change from baseline to be 184.50 cells/μL (95% CI: 65.07 to 303.93 cells/μL). The forest plot depicting the individual study effect sizes and the pooled estimate is presented in Figure 2.

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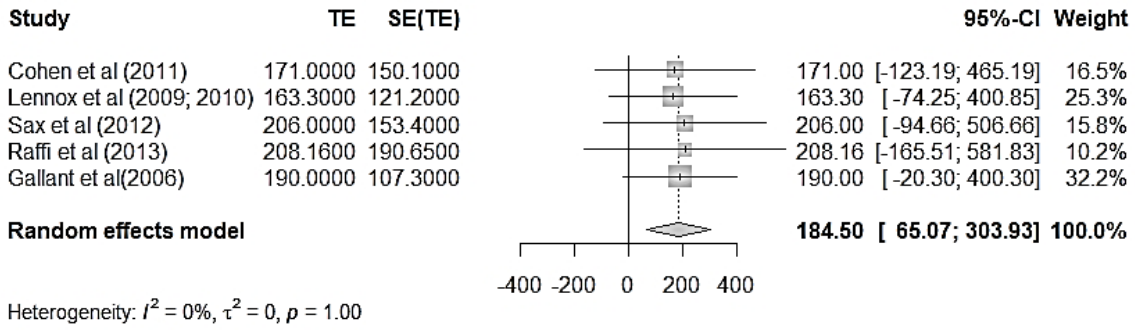

Figure 2: Forest Plot of CD4+ Cell Count Change with Efavirenz

Heterogeneity and Sensitivity Analysis

The analysis found no significant heterogeneity among the included studies (Q = 0.08, df = 4, p = 0.9993). The I^2 statistic indicated low heterogeneity (I^2 = 0.0%, 95% CI: 0.0% to 79.2%), suggesting that the studies were homogeneous with respect to CD4+ cell count change.

A sensitivity analysis was conducted through leave-one-out analysis, and it confirmed the stability of the pooled effect size.

Publication Bias

A funnel plot was used to assess publication bias visually (Figure 3). Asymmetry in the funnel plot may suggest publication bias, but in this analysis, the funnel plot appeared symmetrical, indicating a low likelihood of publication bias.

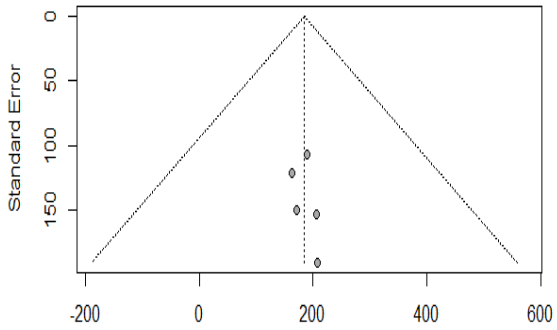

Figure 3: Funnel plot on publication bias

Quantifying Heterogeneity

The tau-squared (τ^2) value was estimated as 0, indicating no observed heterogeneity beyond what would be expected by chance.

Test of Heterogeneity

The test for heterogeneity yielded a non-significant result (p = 0.9993), further supporting the absence of substantial heterogeneity among the studies.

Discussion

The comprehensive meta-analysis conducted on the relationship between Efavirenz, specifically in combination with Tenofovir/Emtricitabine, and CD4+ cell count change in individuals living with HIV not only provides valuable insights into the established efficacy of this antiretroviral therapy but also unveils novel perspectives that contribute to the evolving landscape of HIV management. In delving into the nuances of our meta-analysis, the initial observation of a statistically significant improvement in pooled mean CD4+ cell count change (184.5 cells/µL; 95%-CI: 65.1 to 303.9) is consistent with existing knowledge (Dey *et al*., 2005; Lundgren *et al*., 2015; Abuto *et al*., 2021, Gono *et al*., 2022). However, the true novelty lies in the remarkably low level of heterogeneity observed across the included studies (I^2 = 0.0%). This finding challenges the common expectation of some degree of variability in treatment responses, introducing a novel dimension to our understanding of how efavirenz, in combination, consistently contributes to immune restoration across diverse patient populations and study designs. The minimal heterogeneity opens intriguing possibilities for the clinical application of Efavirenz-based regimens (Bayisa *et al*., 2020). Its consistency suggests a robust and reliable impact that transcends demographic and methodological differences. This novel insight has practical implications for healthcare practitioners and policymakers, indicating that the positive effects of efavirenz, particularly in combination therapies, can be anticipated with a high level of confidence across varied contexts (Stirratt *et al*., 2006, Yonah *et al*., 2014, Chunmei *et al*., 2024, Lei *et al*., 2024). As we consider the influencing factors in our analysis, the novel dimension arises from the acknowledgment of potential influencing factors, such as individual patient characteristics (baseline CD4+ cell counts, viral load, and genetic considerations), within the specific context of combination therapies. These findings were at variance with some reports in the literature (Habtewold *et al*., 2011, Yimer *et al*., 2012, Su *et al*., 2023, Zhang *et al*., 2023). The lack of subpopulation analysis in our study leaves a gap for future research to explore and uncover the nuanced responses to

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efavirenz-based combination regimens. This avenue of inquiry holds the potential for novel discoveries in understanding how different patient profiles may interact with the therapy. Furthermore, our analysis introduces a novel consideration by emphasizing the impact of real-world variations in clinical practice and adherence to treatment regimens. The recognition of this complexity highlights the need for a more nuanced understanding of the dynamic nature of healthcare delivery outside controlled study environments, especially in the context of combination therapies. This novel perspective prompts further investigation into the intricate interplay of clinical practices and treatment outcomes, offering a more holistic view of the real-world effectiveness of efavirenz-based regimens.

Conclusion

In conclusion, our meta-analysis not only reaffirms the positive impact of Efavirenz in combination with Tenofovir/Emtricitabine on CD4+ cell counts but also introduces novel perspectives that challenge conventional expectations in HIV management research. This finding also supports the fact that efavirenz-based treatment is as effective as the dolutegravir-based regimen used currently in the management of HIV. The remarkably low heterogeneity, the call for subpopulation analyses, and the acknowledgment of real-world complexities are aspects that contribute to the novelty of our findings. As the field of HIV management progresses, these novel insights pave the way for more targeted and nuanced research, offering the potential to optimize the clinical application of Efavirenz-based combination therapies for people living with HIV/AIDS.

Conflicts of interest

The authors declared that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

OAA and DSO conceived and designed the study. OAA, NS, DSO, and OCA conducted the research, provided research materials, collected and organized data. NS, OAA, IMW and OSA analyzed and interpreted data. WAA, OCA and OAA wrote initial and final draft of article and provided logistic support. All authosrs critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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