Annals of Clinical and Medical Case Reports

Research Paper

ISSN 2639-8109 | Volume 14

Meta-analysis of first-line Antiretroviral Treatment Failure in Adult HIV Patients in Ethiopia following Implementation of the 'Universal Test and Treat Strategy

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Received: 12 Aug 2024
Accepted: 12 Sep 2024
Published: 17 Sep 2024
J Short Name: ACMCR

Citation:

Feleke SF, Meta-analysis of first-line Antiretroviral Treatment Failure in Adult HIV Patients in Ethiopia following Implementation of the 'Universal Test and Treat Strategy. Ann Clin Med Case Rep. 2024; V14(4): 1-8

Keywords:

First-line; Antiretroviral; Treatment failure; Adult; HIV; Ethiopia

1. Abstract

1.1. Background: With ART programs expanding significantly under test-and-treat strategies, treatment failure is on the rise. In Ethiopia, studies assessing first-line ART failure and associated factors show varying findings, leading to inconsistencies in reported magnitudes.

1.2. Objective: Systematic Review and Meta-analysis on the magnitude and determinants of First-line Antiretroviral Treatment Failure in Adult HIV Patients in Ethiopia Post Implementation of the 'Universal Test and Treat Strategy.

1.3. Methods: The study procedure adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guideline. A thorough search was conducted across databases including PubMed/MEDLINE, Google Scholar, and gray literature. Essential data for the systematic review were gathered and organized using an extraction table in Microsoft Office Excel software. Further analysis was conducted using STATA 17. Heterogeneity among the studies was evaluated through both visual and statistical methods. The protocol has been registered in the PROSPERO-International Prospective Register of systematic reviews under registration number CRD42022378567.

1.4. Result: The combined estimated prevalence of initial ART treatment failure among adult individuals in Ethiopia was found to be 23.50% (95% CI; 11.55, 35.46; I2=99.95%, P≤0.001). Factors such as TB/HIV co-infection (AOR= 4.23, 95% CI: 1.23, 8.23), suboptimal adherence to ART (AOR= 4.84, 95% CI: 3.708, 8.090), and baseline CD4 count less than or equal to 200 (AOR= 7.89, 95% CI: 3.340, 11.201) were positively associated with first-line ART treatment failure.

1.5. Conclusion: Co-occurrence of TB/HIV, initial CD4 count at or below 200, and inadequate adherence to ART were identified as separate factors influencing the likelihood of first-line ART treatment failure in adults. Hence, it's vital for authorities to prioritize interventions targeting these factors to reduce the risk of first-line ART treatment failure.

2. Introduction

HIV, a prevalent chronic health condition, disrupts the body's immune system, impairing its capacity to combat infections[1]. It contributes to a global pandemic and is the underlying cause of acquired immune deficiency syndrome (AIDS)[2]. As per the World Health Organization (WHO) report, in 2021, there were an estimated 38.4 million individuals living with HIV, 1.5 million new HIV infections, and 650 thousand deaths attributed to HIV-related causes[3].

Out of the 1.5 million individuals who contracted HIV in 2021, approximately 1.3 million were adults[3]. Ethiopia is among the

nations significantly impacted by HIV, with a prevalence rate of 1.1%[4].

Antiretroviral therapy (ART) is widely recognized as the standard treatment for HIV patients. It helps to restore immune function and mitigate adverse outcomes associated with HIV infection. [5]. Nonetheless, when treatment fails, this opportunity diminishes, resulting in heightened morbidity and a compromised quality of life for HIV patients[6]. ART failure refers to the advancement of the disease following the commencement of antiretroviral therapy. This progression can manifest through clinical, immunologic, or virological indicators[7]. Nevertheless, given that the primary goal of antiretroviral therapy is to decrease viral load, the efficacy of treatment is most accurately gauged by achieving viral suppression, typically defined as having fewer than 50 copies/ml of the virus[8].

Due to the widespread expansion of antiretroviral therapy (ART) following the test-and-treat era, treatment failure is increasingly prevalent[9, 10]. The occurrence of first-line ART failure varies notably among countries, contingent upon the criteria employed (clinical, immunological, or virological) for its diagnosis[11]. In Africa, the Virological failure rate for first-line ART was recorded at 7.1 per 100 patient-years of follow-up[12]. In Ethiopia, research studies indicate a treatment failure rate ranging from 5.3% to 19% [13, 14].

The World Health Organization (WHO) introduced the "universal test and treat" (UTT) initiative as a strategy for HIV elimination, replacing the previous approach known as "differing treatment," which relied on CD4-based and WHO clinical staging methods[15] [16]. UTT is a program that recommends screening all populations at risk for HIV infection, with those diagnosed as HIV positive receiving early treatment irrespective of their CD4 count or WHO clinical stage. Numerous countries, including Ethiopia, have embraced the 'test and treat' program [17].

Various factors can contribute to treatment failure, including inadequate medication adherence, non-compliance with isoniazid prophylactic therapy, lower baseline CD4 count, being bedridden at the onset of ART, older age, advanced disease stage (III/IV), history of injection drug use, prior use of protease inhibitors, and co-infection with tuberculosis (TB) [18-22].

Several research endeavors have been undertaken in Ethiopia to evaluate the prevalence and factors associated with first-line ART failure in individuals living with HIV [6, 23-26]. Despite several studies conducted in Ethiopia to evaluate first-line ART failure among individuals with HIV, inconsistencies have been observed in the reported findings. This study aims to provide more precise estimates and insights following the adoption of the "Universal Test and Treat" strategy by the Ethiopian Federal Ministry of Health through a systematic review and meta-analysis, it seeks to determine the combined prevalence and associated factors of first-line Antiretroviral Treatment Failure among adult individuals with HIV in Ethiopia.

3. Methods

3.1. Study protocol registration

This systematic review and meta-analysis sought to identify the collective prevalence and factors associated with first-line Antiretroviral Treatment Failure among adult HIV patients in Ethiopia, considering the implementation of the "Universal Test and Treat" strategy. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[27]. The study protocol was registered in the Prospero International Prospective Register of Systematic Reviews under the registration number CRD42022378567.

3.2. Search strategy

Two researchers (NA, SF) conducted a thorough search using MEDLINE/PubMed, Google Scholar, and gray literature databases. The inclusion criteria focused on articles published since 2016, aligning with the implementation of the "Universal Test and Treat" strategy by the Ethiopian Federal Ministry of Health for managing HIV/AIDS. Additionally, additional articles were sought through searches in online university repositories (specifically, the University of Gondar and Addis Ababa University) and by reviewing the reference lists of identified studies. Searches were conducted based on adapted PICO principles, employing Boolean logic and connectors such as "OR" and "AND" to access essential articles from the databases listed above. Various combinations of terms and keywords ("prevalence, incidence, magnitude", "first line", "antiretroviral", "treatment", "failure", "adult", "HIV patients") were utilized separately or in combination with Boolean operators "AND" and "OR". Additionally, hand searching of the reference lists of relevant papers was performed to identify additional articles, which were then screened using the eligibility criteria.

3.3. Eligibility Criteria

The systematic review and meta-analysis outlined specific inclusion criteria. Eligible studies, regardless of publication status, needed to have been conducted post the test-and-treat era and be available in English. They could encompass any study design and had to concentrate on reporting the prevalence and factors associated with treatment failure in adult HIV patients. Studies that did not report the relevant outcome or lacked information on either the magnitude of treatment failure or its associated factors were excluded. Moreover, abstracts-only papers, reviews, conference papers, editorials, case reports, and articles without full PDF access were not considered for inclusion.

3.4. Outcome of measurement

This study evaluated two primary outcome variables. The main focus was on determining the prevalence of Antiretroviral Treatment (ART) failure, utilizing all criteria for confirming ART treatment

failure. This encompassed virological, immunological, or clinical failure. Virological failure was identified when the plasma viral load exceeded 1000 copies/ml in two consecutive measurements within a three-month interval, despite adherence to the ART treatment regimen. Immunological failure was defined as a CD4 count < 250 cells/mm3 following clinical failure or persistent CD4 cell/mm3 levels below 100 cells/mm3. Clinical failure occurred when new or recurrent stage 4 or some stage 3 manifestations occurred after six months of ART initiation. [28], whereas associated factors/determinants for ART treatment failure were the second outcome variable. The odds ratio was calculated for the common factors of the reported studies.

3.5. Study selection

Key and potentially pertinent articles sourced from the aforementioned databases and websites were imported into Endnote X8, and duplicate entries were eliminated. Screening and filtering of articles were conducted by examining the title, abstract, and full PDF of each retrieved article, ensuring alignment with our eligibility criteria.

3.6. Quality assessment and critical appraisal

The evaluation of the chosen articles for inclusion in the systematic review, particularly those meeting the specified inclusion criteria, was performed using the Joanna Briggs Institute (JBI) quality appraisal checklist adjusted for cross-sectional, case-control, and cohort studies[29].

Two sets of reviewers independently conducted the assessment to evaluate the methodological quality of the study and ascertain the extent to which bias may have been addressed in its design, conduct, and analysis. Any disagreements were resolved by a third reviewer, and the reviewers engaged in discussions to reach a consensus. Studies were deemed to be at low risk if they scored 50% or higher in the quality assessment [30].

3.7. Data Extraction and Management

Initially, papers underwent screening based on titles and abstracts, and full texts were scrutinized for any uncertainties. Excluded studies did not meet the selection criteria. Three reviewers (NAT, NS, SFF) independently extracted essential data using a standardized format aligned with PECO questions, resolving any disparities through discussion[31].

Essential information for the systematic review was extracted and condensed using an extraction table in Microsoft Office Excel software. The data extraction tool included details such as the first author(s)' name, country and manufacturing type, study design, year of publication, sample size, and prevalence of treatment failure.

3.8. Data analysis

Data extraction was performed using Microsoft Excel and subsequently transferred to STATA Version 17 Statistical Software for further analysis. Pooled analysis was conducted using a DerSimonian and Laird random-effects model, assuming heterogeneity across studies [32]. Heterogeneity within the included studies was assessed using the I2 test, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Subgroup analysis, based on the study year, was performed in response to observed heterogeneity. Publication bias was evaluated using a funnel plot, as well as Egger's and Begg's tests. Trim and fill analysis was utilized to address any publication bias detected. Meta-analysis results were presented through a forest plot displaying odds ratio (OR) and 95% confidence intervals (CI). All tests were two-sided, with significance set at $p < 0.05$.

3.9. Patient and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

4. Result

4.1. Description of eligible studies

A total of 478 articles were obtained concerning preterm birth through electronic searches. Of these, 183 papers were sourced from PubMed/MIDLINE, 283 from Google Scholar, and 12 from other sources. During the screening of titles and abstracts, 313 duplicate and 152 non-eligible papers were identified and subsequently excluded. The remaining 13 articles underwent a full-text review, resulting in 6 papers being deemed suitable and eligible for analysis. Seven articles were excluded based on the specified exclusion criteria (Figure 1).

4.2. Characteristics of the included studies

Consequently, six studies met the inclusion criteria and proceeded to undergo the final systematic review and meta-analysis. This compilation comprises two cross-sectional, three case-controls, and one cohort study, encompassing a total of 2,317 study participants across various regions in Ethiopia.

4.3. Prevalence of first-line ART treatment failure among adults in Ethiopia

The forest plot (Figure 2) illustrates the overall pooled prevalence of first-line ART treatment failure among adults in Ethiopia. The combined estimated prevalence of first-line ART treatment failure among adults in Ethiopia was 23.50% (95% CI; 11.55, 35.46; I2=99.95%, P≤0.001).

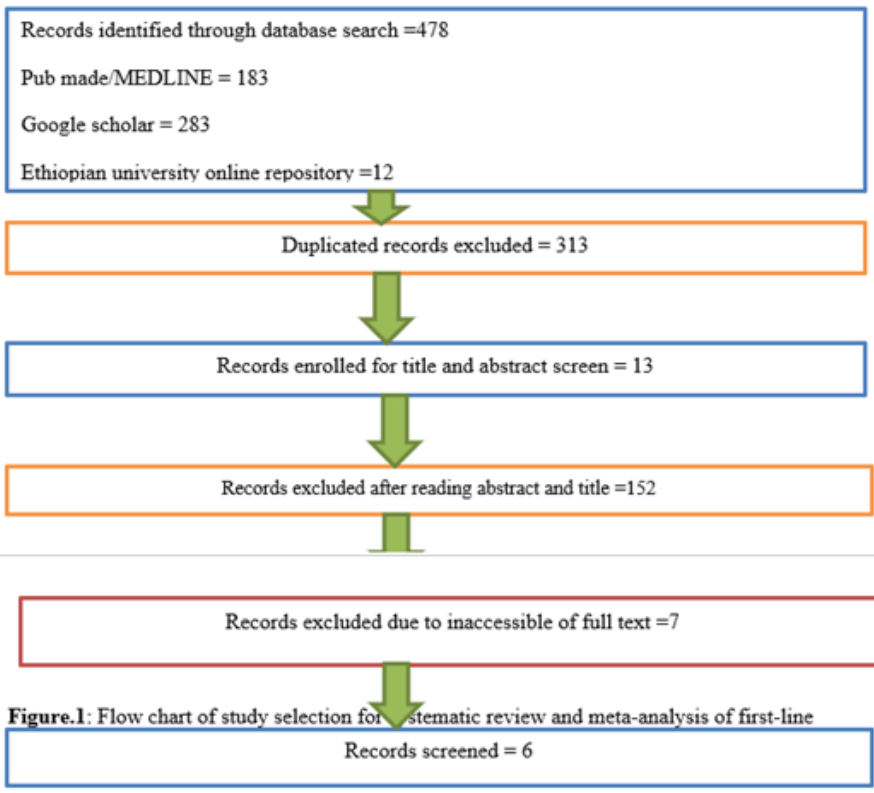

Figure.1: Flow chart of study selection for systematic review and meta-analysis of first-line

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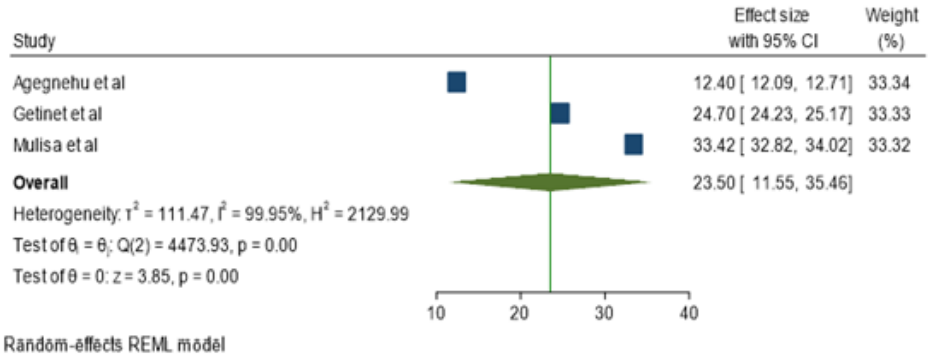

Figure 2: Forest funnel plot of the pooled prevalence of first-line ART treatment failure among adults in Ethiopia

4.4. Subgroup analysis

Subgroup analysis was performed to address the observed heterogeneity, with the Cochrane I2 statistic indicating substantial heterogeneity (I2=99.95%, P≤0.001). Consequently, subgroup analysis was conducted based on the year of publication (≤ 2020) of the articles. According to the subgroup analysis, the prevalence of first-line ART treatment failure among adults in Ethiopia was 22.908% (95% CI: 2.309, 43.508), with substantial heterogeneity still observed (I2=99.7%, P≤0.001). Additionally, the spread of the plotted circles around the regression line in (Figure 3) further indicates heterogeneity among the studies.

4.5. Publication bias

(Figure 4) Displays a funnel plot used to assess the asymmetrical distribution of first-line ART treatment failure among adults in Ethiopia through visual examination. Egger's regression test yielded a p-value of 0.003, indicating the presence of publication bias. Consequently, trim and fill analysis were conducted to address this bias. Following the trim and fill procedure, the pooled prevalence of first-line ART treatment failure among adults in Ethiopia was recalculated to be 16.165% (95% CI 15.905, 16.424).

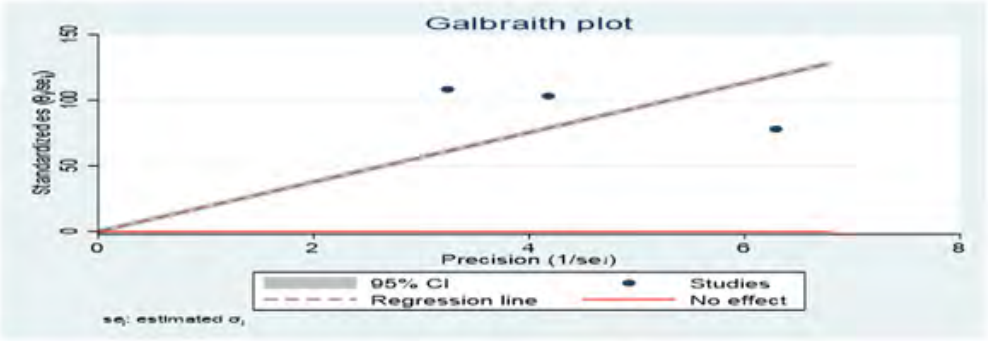

Figure 3: Galbraith plots of the pooled prevalence of first-line ART treatment failure among adults in Ethiopia.

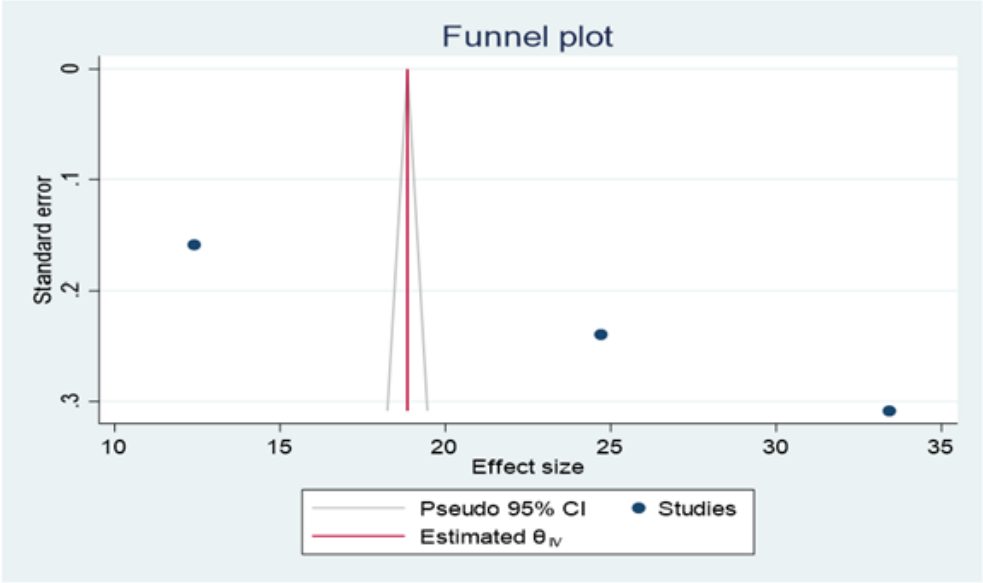

Figure 4: Factors associated with first-line ART treatment failure

4.6. Factors associated with first-line ART treatment failure

The systematic review and meta-analysis identified several risk factors associated with first-line ART treatment failure among adults in Ethiopia. These factors include TB/HIV co-infection, baseline functional status, educational status, adherence, NNRTI ART-based treatment, and baseline CD4 count. Adults with TB/HIV co-infection showed a positive association with first-line ART failure (AOR= 4.23, 95% CI: 1.23, 8.23). High heterogeneity (I2 =79.02, P-value= 0.003) was observed among the included studies, leading to the utilization of a random-effects model. Moreover, Egger's test did not detect any indication of publication bias, with a p-value of 0.89. Poor adherence to ART (AOR= 4.84, 95 CI: 3.708, 8.090) was a predictor for first-line ART failure among adults in Ethiopia. High heterogeneity (I2= 92.4, P-value =0.004) was identified among included studies. Due to this reason, the random effect model was calculated. Moreover, the possibility of publication bias was not detected using Egger's test with a p-value of 0.982. Adults with a baseline CD4 count of 200 or less were positively associated with first-line ART treatment failure (AOR= 7.89, 95% CI: 3.340, 11.201). High heterogeneity (I2 =78.98, P-value =0.023) was observed among the included studies, leading to the use of a random-effects model. Additionally, Egger's test did not indicate any evidence of publication bias, with a p-value of 0.564(Supplemental table).

Table 1: Study characteristics included in the systematic review and meta-analysis in Ethiopia (n = 6)

Authors	Publication year	Study design	Study region	Sample size	Prevalence	Quality
Agegnehu[24]	2020	Retrospective follow –up	Amhara	490	0.124	Low risk
Ahmed [33]	2019	Case control	Amhara	308	NA	Low risk
Getinet [23]	2021	Cross-sectional	Amhara	430	0.247	Low risk
Meshesha [26]	2020	Case control	Amhara	389	NA	Low risk
Diriba Mulisa[34]	2019	Case control	Oromia	350	NA	Low risk
Diriba Mulisa[35]	2020	Cross-sectional	Oromia	350	0.3342	Low risk

5. Discussion

In resource-constrained settings, addressing first-line ART failures poses a significant challenge for HIV programs. Persisting on failing first-line therapy is associated with an increased risk of mortality. Furthermore, the emergence of drug resistance hampers the development of effective and tolerable regimens in the future.

In this meta-analysis, the overall pooled prevalence of first-line ART treatment failure among adults in Ethiopia was 23.50 % (95% CI; 11.55, 35.46; I2=99.95%, P≤0.001). This finding is higher than the studies done in India (7.69%), Tanzania in which the failure rate was 7% [36] and a study conducted in South Africa that reported a failure rate of 2.1% [37]. The discrepancy in this magnitude might be due to the differences in living conditions of the population, sample size difference, difference in study design, and year of the study.

In this study, individuals with TB/HIV co-infection were 4.23 times more likely to experience first-line ART treatment failure. This suggests that tuberculosis may accelerate the advancement of HIV infection. Various studies have indicated that patients with HIV-TB co-infection exhibit poor recovery of CD4+ T-cells. Additionally, severe CD4+ T-cell depletion, lymphocytopenia, and compromised immune restoration were observed in HIV-TB patients[38][39].

Furthermore, reduced adherence to HIV treatment during TB treatment, due to the high pill burden and side effects, may exacerbate viral replication [40].

Therefore, individuals newly diagnosed with HIV should undergo early and frequent TB screening and testing, and efforts should be made to minimize the time between diagnosis and treatment initiation.

This study showed that the odds of first-line ART treatment failure were fivefold higher in clients who had poor adherence to ART compared with those who had good adherence. Similarly, studies conducted in Mozambique [41], Nigeria[42], Uganda[43] and Tanzania[44] showed that poor adherence increased the odds of first-line ART treatment failure. This phenomenon can be attributed to adherence to ART drugs, which effectively suppress viral replication and consequently increase CD4 cell count. Conversely, poor adherence leads to heightened viral replication, resulting in increased infection of CD4+ cells and subsequent depletion of their numbers. Additionally, adults may encounter various challenges including treatment failure, drug resistance, and the onset of opportunistic infections, all of which can contribute to poor treatment outcomes. Therefore, offering treatment adherence counseling to adults at the initiation of treatment and during follow-up periods would be beneficial.

The findings revealed a significant association between having a baseline CD4 count less than 200 cells/mm3 and first-line ART treatment failure among adults. This study findings was consistence with other studies as determinants of first line ART treatment failure conducted in Zimbabwe [45], Tanzania, South Africa[46] and China[47]. This is attributed to the fact that CD4 T cells are the primary target cells for HIV infection. A decrease in CD4 cell count increases the likelihood of opportunistic infections and subsequent clinical failure. Additionally, low CD4 levels correlate with high viral loads, leading to virological failure. It's challenging to sufficiently boost initial low CD4 counts in HIV-infected patients, which can also result in immunologic failure. Conversely, higher CD4 levels help prevent opportunistic infections and reduce viral load.

This study reported significant heterogeneity. It's worth noting that a high I2 value doesn't always indicate substantial heterogeneity. In cases like this study, where only a small number of studies with no true heterogeneity are included in the meta-analysis, the I2 statistic may overestimate heterogeneity [48][49].

6. Limitation

This review was restricted to articles published exclusively in English, potentially introducing reporting bias. Additionally, data were not available from all regions of the country, potentially leading to issues with representativeness.

7. Conclusion and Recommendation

The combined prevalence of first-line ART treatment failure among adult patients in Ethiopia is notably high. TB/HIV co-infection, baseline CD4 count of 200 or less, and poor adherence to ART emerged as independent factors associated with first-line ART treatment failure among adults. Consequently, it is imperative for all relevant authorities to address these identified factors diligently to mitigate the risk of first-line ART treatment failure.

8. Acknowledgment

The authors of the primary study are acknowledged.

9. Authors' contributions

SFF and NAT worked on conceptualization, BMY, NS and SFF data analysis. BMY, NAT wrote the main manuscript text. SFF ,TE and NS edit the final manuscript. All authors reviewed the manuscript.

All authors made considerable contributions to conception and design, acquisition of data, or evaluation and interpretation of data; took section in drafting the article or revising it significantly for necessary intellectual content; agreed to put up to the current journal; gave ultimate approval of the version to be published; and agree to be responsible for all elements of the work.

10. Competing interests

All authors declare that they have no competing interests.

11. Ethics and consent

Not applicable

12. Funding

No funding was obtained for this study

13. Paper context

Not applicable

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