Incidence and Determinants of Mortality among Adult Patients Taking Antiretroviral Therapy in Ethiopia: Systematic Review and Meta-Analysis

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Research

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Abstract

Reduced AIDS mortality has been linked to the advent of highly active antiretroviral medication. The previous reviews conducted in Ethiopia lack the overall rigor and clarity in the study methodology, reported results and statistical inference. The goal was to create a data summary from studies accomplished previously throughout the nation so that programmers and implementers could use to harmonize the current advanced intervention and direct health service providers to improve ART service provision packages. This data would provide a thorough update on the magnitude of mortality among HIV-infected patients taking HAART by combining 21 eligible articles. The study’s heterogeneity, publication bias, and quality were examined. The statistical analysis used random-effects model in STATA version 14. The protocol was registered(CRD42019123380).

As a result, the pooled mortality incidence was 5 per 100 person-years of observation (95% CI: 4–5 per 100 pyo). Two-thirds of deaths occurred within the first year of starting HAART. Clinical stage (Pooled HR = 3.15; 95% CI: 2.36–4.21), CD4 count (Pooled HR = 2.31; 95% CI: 1.83–2.93), hemoglobin level (Pooled HR = 3.05; 95% CI: 2.19–4.27), TB co-infection (Pooled HR = 3.08; 95% CI: 2.21–4.29), and functional status (Pooled HR = 4.86; 95% CI: 3.59–6.97) were factors in this study that were substantially linked to higher mortality. Mortality rates were high, especially early in the therapeutic process. Significant mortality risk factors were WHO clinical stage, CD4 count, poor hemoglobin, TB co-infection, and non-working functional status. This significant mortality rate could be avoided with comprehensive care and stringent monitoring.

1. Introduction

Rational of the study

Infection with the Human Immunodeficiency Virus (HIV) has rapidly expanded around the world and is now one of the biggest threats to public health in many nations (1). Since the beginning of the epidemic in 1981, 77 million individuals have acquired HIV, and 35 million have died from it. In the adult population, there are 35 million people who are HIV-positive and 1.62 million people who are newly infected. Each year, over 830 000 adults died from these causes (2).

Worldwide, one-fourth of HIV-positive people still require access to HIV testing services. Antiretroviral medication (ART) was available to 21.7 million people living with HIV (59%) in 2017, an increase of 2.3 million from 2016 and 8 million from 2010 (3). In 2017, there were 25.7 million HIV-positive people worldwide (69%): 5.2 million in Asia and the Pacific, 5.2 million in Africa, and 2.2 million in Europe and North America (3,4).

The advent of HAART and the high caliber of comprehensive advanced client-centered services are two factors that have contributed to a progressive decline in the global trends of HIV-related mortality throughout time (5). Since 2010, AIDS-related mortality has decreased 34% globally, but more reductions of almost 150 000 deaths annually are needed to attain the 2020 milestone (4). There are 25.92 million
HIV-positive persons living throughout all of Africa. In 2017, there were around 1.2 million new AIDS-related infections and 669,800 AIDS-related deaths. Regions in Sub-Saharan Africa accounted for over 66% of the disease's global burden (3).

In Ethiopia, there were 678,165 people living with HIV, 20,551 people contracted the virus that year, and 9,294 people died each year (5). Researches revealed that two years after ART was introduced, the rate of AIDS mortality decreased by 50% and the mortality rate attributed to AIDS decreased from 50% to 14% for women and 40% to 11% for men between 2001 and 2009 (6,7).

Many HIV-positive individuals lack access to prevention, treatment, care, and support services. In addition to affecting the health of individuals, homes, communities, and entire countries, HIV primarily affects the most productive age group. Numerous of the nations most affected by HIV also experience significant difficulties as a result of other infectious diseases, food instability, and other issues with global health and development (5). Evidence-based data should be used to support the global initiative to ensure that every person is free of HIV, free from discrimination, treated with dignity, equality, and health, and that those who are HIV-positive receive the care and support they need to survive and improve the quality of their lives (5–7).

Over the past thirty years, the Ethiopian government has continued to prioritize combating HIV/AIDS as one of its top health goals. Ethiopia now has a multi-sectoral strategy to combat HIV/AIDS, involving the community and working with domestic and international partners. However, the epidemic was only partially controlled by initiatives that were too small in scope, lacked coordination, and were primarily attributed to the health sector (2,5–7).

The clinical benefit of HAART for HIV-infected patients, in terms of mortality reduction and improved quality of life, is well established, but it varies regionally, with a higher incidence of mortality within the first years of HAART initiation, especially during the first 3 to 6 months of treatment, and the factors contributing to this high mortality are poorly understood (8).

Many factors, such as CD4 count, total lymphocyte count, body mass index, adherence to medicine, WHO clinical stage, number of years with the virus, and the presence of opportunistic infections, determine mortality for HIV-infected patients starting HAART. Numerous studies carried out in Ethiopia revealed that the factors influencing mortality from AIDS-related illnesses varied. In order to decrease excess mortality, change morbidity, and enhance quality of life for HIV-infected patients, a better understanding of the determining factors would enable tighter follow-up and more targeted therapies (9–12).

As a result, it is critical to investigate the incidence and the determining factors for death among HIV-positive people. This review will offer higher-quality, evidence-based data that are essential for the healthcare system, in particular the ART program, to make the necessary corrections as a remedy.

**Objective of the Study**
HIV/AIDS has remained a major public health concern across the world, particularly in Sub-Saharan African countries such as Ethiopia. The approach to this critical public health issue must be vigorous and thorough, with evidence of efficacy analysed and examined on a regular basis. Timely access to high-quality data from surveys, surveillance, national reports, programme evaluation reports, standardised recommendations, and diverse investigations is essential to guarantee that programme responses are appropriate to the nature of the epidemic. More comprehensive, systematic, scientifically reliable, and precise evidence is clearly needed to assist the HIV programme response in controlling the epidemic and reaching the ambitious goal of eradicating AIDS.

However, in reality, access to such data remains a serious barrier in underdeveloped nations such as Ethiopia. There were several single studies done around the country during the early search. When they are combined, they form summary data/evidence for disease control. There were no studies in Ethiopia that reported the aggregated measure of incidence and determinants of death in HIV-infected adult patients on antiretroviral treatment. This research will examine all existing reliable and accessible data on the incidence and determinants of mortality due to HIV/AIDS-related disease in Ethiopia in order to allow their use during the design, planning, programming, and evaluation of interventions. The result of this study would improve the available data on the incidence and determinants of mortality among HAART patients in Ethiopia, as well as to provide valuable data that will be an important milestone for intervention, policy making, and a reference for scholars and students. Hence, the primary goal of this research was to determine the pooled incidence and determinants of death among HIV-infected adult patients who had begun HAART in Ethiopian health institutions.

2. Methods

Eligibility criteria

This systematic review and Meta-analysis considered all those published and unpublished cohort studies conducted throughout country (Table 1). The inclusion criteria are evaluated based on the COCOPO principle adapted from the Joanna Briggs Institute Reviewer’s Manual of 2017.

As a result of the above inclusion and exclusion criteria indicated in the table; studies with the interest of outcome on the incidence and determinants of mortality, those cohort studies conducted on adult population and at any health institutions in the nation were included in the analysis. On the other hand, studies that did not include the interest of the outcomes, program evaluation studies, studies including adult HIV-infected patients receiving pre-ART service, and studies that did not give all necessary information or missed data were all disregarded from the analysis.

Information sources

For the purpose of obtaining studies, openly accessible databases and institutional repositories of the university and research center were combed through. Google Scholar, PubMed, Scopus, Cochrane Library,
and Directory of Open Access Journal were the databases used as information source. The Addis Ababa, Gonder, Jimma, Haramaya, Bahir Dar, and Hawassa Universities are among the institutions whose archives being searched for unpublished research. The Economic Commission for Africa, the African Union, the National Academic Digital Repository of Ethiopia, and other research center organizations were searched for papers on their repositories. The search was carried out from March 15 through April 30, 2019.

**Literature Searching strategy**

A thorough internet search was conducted to discover research articles in electronic databases using the boolean operators coupled with keywords and MESH terms illustrated in the table 2 & 3. A hand-search was also performed by reading through the reference lists from the studies that were included in the automated search. The search period was limited to journal articles conducted from January 1, 2005 through April 30, 2019 and written in English. The outcomes of the manual search in the institutional repositories and the electronic publically accessible databases were integrated for subsequent selection. (Table 2 & 3)

<table>
<thead>
<tr>
<th>S.N</th>
<th>Searching Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV [tw] OR &quot;human immunodeficiency virus&quot; [tw] OR AIDS[tw] OR &quot;acquired immunodeficiency syndrome&quot;[tw]</td>
</tr>
<tr>
<td>3</td>
<td>HAART [tw] OR &quot;highly active antiretroviral therapy&quot;[tw] OR &quot;highly active anti retroviral therapy&quot; [tw]</td>
</tr>
<tr>
<td>4</td>
<td>&quot;Antiretroviral Therapy, Highly Active&quot;[Mesh]</td>
</tr>
<tr>
<td>5</td>
<td>Ethiopia[tw]</td>
</tr>
<tr>
<td>6</td>
<td>&quot;Ethiopia&quot;[Mesh]</td>
</tr>
<tr>
<td>7</td>
<td>Incidence [tw] OR determinant*[tw] OR risk*[tw] OR predictor*[tw]</td>
</tr>
<tr>
<td>8</td>
<td>&quot;Incidence&quot;[Mesh] OR &quot;Epidemiologic Factors&quot;[Mesh]</td>
</tr>
<tr>
<td>9</td>
<td>Mortality[tw] OR Death*[tw] OR survival[tw]</td>
</tr>
</tbody>
</table>

Table 3: Detail of advanced search strategy sampled on Pubmed search engine
<table>
<thead>
<tr>
<th>Search</th>
<th>Recent queries</th>
<th>Items found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search (Ethiopia[tw]) OR &quot;Ethiopia&quot;[Mesh]</td>
<td>15013</td>
<td></td>
</tr>
<tr>
<td>Search (((HAART [tw] OR &quot;highly active antiretroviral therapy&quot;[tw] OR &quot;highly active anti-retroviral therapy&quot; [tw]))) OR &quot;Antiretroviral Therapy, Highly Active&quot;[Mesh])</td>
<td>26073</td>
<td></td>
</tr>
<tr>
<td>Search (Mortality[tw] OR Death*[tw] OR survival[tw])</td>
<td>2339858</td>
<td></td>
</tr>
<tr>
<td>Search (&quot;Incidence&quot;[Mesh] OR &quot;Epidemiologic Factors&quot;[Mesh])</td>
<td>1598019</td>
<td></td>
</tr>
<tr>
<td>Search (Incidence [tw] OR determinant*[tw] OR risk*[tw] OR predictor*[tw])</td>
<td>3263229</td>
<td></td>
</tr>
<tr>
<td>Search &quot;Ethiopia&quot;[Mesh]</td>
<td>10968</td>
<td></td>
</tr>
<tr>
<td>Search Ethiopia[tw]</td>
<td>15013</td>
<td></td>
</tr>
<tr>
<td>Search &quot;Antiretroviral Therapy, Highly Active&quot;[Mesh]</td>
<td>20216</td>
<td></td>
</tr>
<tr>
<td>Search (HAART [tw] OR &quot;highly active antiretroviral therapy&quot;[tw] OR &quot;highly active anti-retroviral therapy&quot; [tw])</td>
<td>26073</td>
<td></td>
</tr>
</tbody>
</table>
Study Selection

After duplicate studies were eliminated, all retrieved studies were forwarded to Thomson Reuters' Endnote X3 reference manager system. The remaining publications were inspected based on their titles and abstracts, and then full-text evaluation was established to determine their eligibility. Finally, studies that matched the requirement were included in the analysis.

Data Collection Process

A standardized data extraction sheet was used to obtain the quantitative data from the review papers. Two reviewers have cross-checked the data from all included studies to ensure their consistency. The author and year of publication, study area, study subjects, study design, total sample size, number of participants and events per group, median follow-up period, incidence of mortality due to AIDS-related causes, and Hazard Ratio between exposed and non-exposed groups were extracted using the extraction sheet. The reviewers employed identical data extraction methodologies. The Joanna Briggs Institute (JBI) Meta-Analysis of Statistics Assessment and Review Instruments were used to assess the quality of each study included in the final analysis.

Data Items

Incidence of mortality: the main outcome of interest of this study was determining the incidence of mortality among HIV infected patients. It was calculated by dividing the number of events/deaths occurred due to HIV/AIDS in a specified period of time per person years of observation.

Determinants of mortality: variables which are associated with mortality. These might included WHO clinical stage, CD4+ cells count, co-infection with OI like TB, Adherence to ART medication, functional status of the patients, presence of Anemia, Body weight, prophylaxis to OI, age and gender.

Summary measures
The main outcome of this study was to estimate the incidence of HIV/AIDS-related mortality in Ethiopia, which was measured as the incidence rate, or the ratio of participant deaths during the follow-up period to the total number of person years of observation (events/person years of observation). All potential determinant factors were screened in the studies, and some of them included the patient’s age, sex, WHO clinical stage, CD4+ cells count, adherence to prescribed ARV drugs, functional status, anemia, body weight, year of virus infection, opportunistic infection, including tuberculosis, drug and alcohol use, and nutritional status. To increase the reliability of this review and analysis, determinant factors reported at least in two studies were taken into consideration for further analysis.

**Synthesis Method**

The overall pooled mortality rate and its 95% confidence interval were calculated using the DerSimonian and Laird methods of random-effect model. The incidence of mortality and its factors were compared using the pooled hazard ratio. The Cochrane Q test was used to assess heterogeneity across studies and Higgins and Thompson’s $I^2$ statistic was used to quantify it. To investigate the various sources of heterogeneity, subgroup and sensitivity analyses were done. The funnel plot and Egger’s regression test were used to assess publication bias across studies. All statistical analyses were performed using STATA software version 14. The analysis results were summarized using tables and Forest Plot graphically.

**3. Results**

**Study Selection**

About 463 articles were found using a comprehensive search on database and repositories. After removing duplicate retrievals, there were 423 articles left. About 300 of them were taken off due to exclusion criteria established throughout the assessment. The final synthesis includes 21 articles in total after a review of the full text articles as shown in the PRISMA flow diagram. (Figure 1)

**Study Characteristics**

The investigations included 23904 participants in total, ranging in age from 152 to 5664, which resulted in 63,107 person-years of observations during the course of their follow-up. About 13390 of them (or 56% of the participants) were women and 2,804 incidents took place during the follow up period. A total of 1154.75 months of follow-up were included in the study; the median follow-up length was 60 months, with a range of 55 weeks to 96 months. Based on the study area, six articles were conducted in Oromia, five in the Southern region, six in the Northern region, and four in the Addis Ababa region. The sample size ranged from 176 in the southern region (13) to 3228 in the northern region (14). The absolute number of deaths registered in the included articles ranged from 24 to 473 in the southern region (19, 22).
southern part of the country had the most articles with large samples (n = 9872), but the northern part of the region had the most interest in the outcome (event = 991) (table 4).

Table 4 study characteristics that showed year of publication, study area, sample size, event and outcome variables

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Study Region</th>
<th>Sample size</th>
<th>Event</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Oromia</td>
<td>446</td>
<td>30</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2010</td>
<td>Oromia</td>
<td>300</td>
<td>28</td>
<td>4.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2018</td>
<td>Oromia</td>
<td>691</td>
<td>91</td>
<td>4.0 (3.0 – 5.0)</td>
</tr>
<tr>
<td>2015</td>
<td>Oromia</td>
<td>2156</td>
<td>120</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2012</td>
<td>Oromia</td>
<td>1623</td>
<td>86</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2017</td>
<td>Oromia</td>
<td>522</td>
<td>66</td>
<td>5.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2016</td>
<td>Southern</td>
<td>2374</td>
<td>196</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2006</td>
<td>Southern</td>
<td>176</td>
<td>24</td>
<td>4.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2016</td>
<td>Southern</td>
<td>385</td>
<td>35</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2015</td>
<td>Southern</td>
<td>822</td>
<td>92</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2011</td>
<td>Southern</td>
<td>6115</td>
<td>473</td>
<td>4.0 (3.0 – 5.0)</td>
</tr>
<tr>
<td>2013</td>
<td>Northern</td>
<td>901</td>
<td>261</td>
<td>4.0 (3.0 – 5.0)</td>
</tr>
<tr>
<td>2014</td>
<td>Northern</td>
<td>566</td>
<td>46</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2014</td>
<td>Northern</td>
<td>1296</td>
<td>366</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2014</td>
<td>Northern</td>
<td>441</td>
<td>54</td>
<td>5.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2012</td>
<td>Northern</td>
<td>3228</td>
<td>216</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2017</td>
<td>Northern</td>
<td>686</td>
<td>48</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2015</td>
<td>Addis Ababa</td>
<td>975</td>
<td>75</td>
<td>5.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2014</td>
<td>Addis Ababa</td>
<td>453</td>
<td>37</td>
<td>5.0 (4.0 – 6.0)</td>
</tr>
<tr>
<td>2012</td>
<td>Addis Ababa</td>
<td>1100</td>
<td>199</td>
<td>5.0 (4.0 – 5.0)</td>
</tr>
<tr>
<td>2009</td>
<td>Addis Ababa</td>
<td>1440</td>
<td>360</td>
<td>5.0 (4.0 – 5.0)</td>
</tr>
</tbody>
</table>

Incidence of Mortality

Data on the incidence of mortality among HIV infected individuals were gathered from 18 articles. The pooled incidence of mortality estimated by using random effect method was found to be five deaths per 100 person-years of observation (95% CI: 4.00–5.00/100pyo) (Figure 2).
Subgroup analysis of studies

According to the year of publication, the death rate among HIV-positive patients was 8 per 100 person-years of observation (95% CI: 6.00-11.00/100 pyo) from 2005 to 2010. There was no statistically significant difference between 2011 and 2014 (incidence rate = 4 per 100 pyo; 95% CI: 3.00-6.00/100 pyo, p-value 0.01; heterogeneity $I^2 = 98.49\%$) and 2015 to 2019 (incidence rate = 4 per 100 pyo; 95% CI: 3.00-5.00/100 pyo, p-value 0.01; heterogeneity $I^2 = 95.43\%$). Based on study area, the southern region (5.00/100; 95% CI: 3.00 - 8.00/100) and Oromia (5/100; 95% CI: 3.00 - 6.00/100) had higher mortality rates than the northern (4/100; 95% CI: 2.00 - 6.00/100) and Addis Abeba (4/100; 95% CI: 4.00 - 5.00/100). Even after conducting a subgroup analysis based on publication year, sample size and study area, there remained significant heterogeneity. As a result, these moderators were ruled out as a source of heterogeneity (Table 5).

Table 5: subgroup analysis in adult HIV infected patients by publication year, sample size and study area

<table>
<thead>
<tr>
<th>Variables</th>
<th>Characteristics</th>
<th>Included study</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>Before 2010</td>
<td>2</td>
<td>8.00 (6.00 – 11.00/100)</td>
</tr>
<tr>
<td></td>
<td>2010 – 2015</td>
<td>8</td>
<td>4.00 (3.00 – 6.00/100)</td>
</tr>
<tr>
<td></td>
<td>After 2015</td>
<td>8</td>
<td>4.00 (3.00 5.00/100)</td>
</tr>
<tr>
<td>Study area</td>
<td>Oromia region</td>
<td>6</td>
<td>5.00 (3.00 – 6.00/100)</td>
</tr>
<tr>
<td></td>
<td>Southern</td>
<td>5</td>
<td>5.00 (3.00 – 8.00/100)</td>
</tr>
<tr>
<td></td>
<td>Northern</td>
<td>5</td>
<td>4.00 (2.00 – 6.00/100)</td>
</tr>
<tr>
<td></td>
<td>Addis Ababa</td>
<td>2</td>
<td>4.00 (4.00 – 5.00/100)</td>
</tr>
<tr>
<td>Sample size</td>
<td>&lt; 1000</td>
<td>12</td>
<td>6.00 (4.00 – 7.00/100)</td>
</tr>
<tr>
<td></td>
<td>≥ 1000</td>
<td>6</td>
<td>3.00 (2.00 – 5.00/100)</td>
</tr>
<tr>
<td>Overall Pooled</td>
<td></td>
<td>18</td>
<td>5.00 (4.00 – 5.00/100)</td>
</tr>
</tbody>
</table>

Sensitivity analysis of incidence of mortality

The leave-one-out sensitivity analysis has been carried out in order to further investigate the probable cause of variability in the study of the incidence of mortality. The results of the analysis had good supporting evidence because the sensitivity analysis revealed that the findings of this study were not dependent on any other studies. After excluding each study individually from the analysis, the pooled estimated incidence of mortality was 4.0 – 5.0 (95% CI: 3.0 – 7.0) deaths per 100 person-years of observation (figure 3).
Determinants associated with incidence of mortality among adult on HAART

WHO Clinical Stage of the Patients

Eighteen studies declared that advanced clinical stage was significantly associated with the increased number of death among HIV infected clients. Three times as many patients with WHO clinical stages III or IV had an early death as those with stages I or II. In patients with WHO clinical stage III or IV, the pooled hazard ratio was 3.15 (95% CI: 2.36–4.21). There was no publication bias in egger's test (p = 0.64) (figure 4).

Baseline CD4 Cells count

Eleven studies showed that CD4 cell count is one of the determinant factor associated with the incidence of mortality among HIV infected individuals. This meta analysis also revealed that the initial CD4 cell count was found to be significantly related to mortality. Patients presented with low CD4 cell counts (< 200/ml) at the start of HAART had twice more to die than their counter parts. The overall pooled hazard ratio was 2.31 (95% CI: 1.83–2.93; p-value < 0.001). There was no publication bias in egger's test (p = 0.77) (figure 5).

Functional Status

Twelve studies confirmed that functional status of HIV patients was significantly associated with mortality. At baseline, people presented with a bedridden functional status were nearly five times more likely to die than other people. Patients presenting with a bedridden functional status had an overall pooled hazard ratio of 4.86, which was higher than that of patients presenting with a working functional status (95% CI: 3.39–6.97) with p-value of 0.001 and heterogeneity $I^2 = 92\%$). There was no publication bias in egger's test with p = 0.491. (Figure 6)

Tuberculosis co-infection

Eleven studies have shown that there was an association between tuberculosis comorbidities and HIV related death. This meta analysis revealed that HIV infected patients presented with TB were three times more likely to pass away than TB uninfected individuals. The pooled hazard ratio was 3.08; 95% CI: 2.21–4.29 with $I^2 = 92.1\%$ with no publication bias (p = 0.37) (figure 7).
Anemia

Nine studies revealed that the base line hemoglobin level has significantly associated with HIV related death among HIV positive clients who started HAART. Patients presented with low hemoglobin levels at the start of HAART had an overall pooled hazard ratio of 3.05 (95% CI: 2.19 – 4.27, p-value < 0.001 and heterogeneity $I^2 = 85.7\%$) (figure 8).

Meta Regression

A meta regression was conducted using sample size, study area and publication year to detect the possible source of heterogeneity between studies. According to the estimated regression there is no proof of that the included studies have significant heterogeneity between them (Table 6).

Table 6: meta-regression test assessing for the source of heterogeneity in the incidence of mortality on adult patients with sample size, study area and publication year

<table>
<thead>
<tr>
<th>Heterogeneity source</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>.0732828</td>
<td>.653433</td>
<td>0.911</td>
</tr>
<tr>
<td>Study area</td>
<td>.2280739</td>
<td>.27377595</td>
<td>0.405</td>
</tr>
<tr>
<td>Publication year</td>
<td>.2158387</td>
<td>.4312213</td>
<td>0.617</td>
</tr>
</tbody>
</table>

Publication bias

Even if the funnel plot of this systematic review and meta analysis showed that the studies were scattered asymmetrically, the regression test for small study effects showed that there was no significant publication bias among the studies (figure 9). The egger’s test (p = 0.158) and begg’s (p = 0.850)

4. Discussion

According to this study, the overall pooled incidence of mortality among adult HIV-positive patients using HAART in Ethiopia was 5 per 100 PYO (95% CI: 4-5 per 100 PYO). This study showed 4 deaths per 100 people aged 15 or older in 2018, down from 8 death rates in the 2010. This showed that the death rate among HIV-infected people has been decreasing over time. This may be the result of better health care delivery systems, government and stakeholder commitments to achieving the global goal, and enhanced patient quality of life as a result of individual level treatment, care and support (2,6,30). When compared to a systematic review and meta-analysis conducted in the Central African Republic (9.1/100 PY, South Sudan 8.2/100 PY, Côte d’Ivoire 7.5/100 PY, Cameroon 7.2/100 PY, Chad 7.1/100 PY, and Nigeria 6.5/100
The pooled incidence of death in this review was lower. The variation may result from differences in the research environment, the populations’ cultures, economic conditions, levels of awareness, and educational backgrounds of the patients (31,32). Nevertheless, it was greater than the Botswana National Program research, which showed a lower mortality rate of 2.06 deaths per 100 person-years of observation over a total follow-up period (32). Differences in the follow-up time, early HIV infection detection and diagnosis, early rapid ART initiation within a week have been observed between the two studies. Putting newly HIV diagnosed patients on HAART before CD4 deterioration and advanced WHO clinical stage began earlier in 2002 in Botswana. These factors could also account for the difference in the estimation. The outcome of this study is consistent with a trend study of deaths among HIV-infected adults receiving ART between 1999 and 2017 in the Asia-Pacific area, which showed that the overall incidence rate of mortality over the follow-up period was 0.28 per 100 pyo. Additionally, in the Asia-Pacific region, the incidence rates of AIDS-related mortality have dropped from 0.51/100 PYO in the year groups 2003–2007 to 0.09/100 PYO in the year groups 2013–2017 (p 0.001) and from 7–2% in Botswana in the years 2002–2012 (32,33). The introduction of effective free HAART to all HIV-infected patients before the decline in CD4 cells and the development of AIDS stages have been associated with improvements in the reduction of mortality over time. This prolongs the time between AIDS deaths and decreases the overall number of AIDS deaths (34).

Patients who had an advanced AIDS stage, a low CD4 cell count, a low hemoglobin level, the presence of TB co-morbidities, non-working functional status at the time of HAART initiation were significantly more likely to die than their counterpart. When starting HAART, HIV-infected adult patients in WHO clinical stages III and IV had about three times the risk of dying compared to individuals in stages I and II. According to research conducted in LMIC (low and middle-income countries) and Tanzania, the majority of patients who died had advanced HIV disease stage, with an OR of 2.3 (95% CI, 1.0 – 5.5) (33,35). Even after starting HAART, people with advanced HIV illness are still at high risk of opportunistic infections and a higher risk of death. The chance of developing a deadly form of advanced HIV disease has regularly been demonstrated to rise with severe immune suppression. Reduced morbidity and a lower mortality rate among patients with advanced WHO clinical stages of the disease will result from early therapy commencement before the onset of those stages (33,35,36). Individuals started HAART with low CD4 cell counts (200 cell/ml) were nearly twice as likely to have a death risk as those with higher CD4 cell counts. Anglemyer’s et al systematic review and meta-analysis (34), studies in Iran (37), Botswana (32) and Tanzania (35) and in-trend mortality analyses in the Asia-Pacific region (33) all support this finding. There are a number of health advantages to starting HAART right now for all HIV-positive patients irrespective of CD4 cell levels. These may include lowering the risk of mortality, delaying the onset of AIDS, increasing the likelihood of immunological recovery (CD4 T-cell counts reaching 800 cells/mm3 or higher after HAART), raising the proportion of people who experienced rapid viral suppression, and extending patient survival and quality of life (33,35,38).

Patients who started HAART in Ethiopia with a non-working functional status were five times more likely to die than those who had a working functional status. Reduced physical performance among HIV-infected people has been linked to increased mortality, according to a study conducted in Maryland, USA.
(HR = 2.52, 95% CI: 1.59–4.00) (39). Due to muscle loss, altered body composition, decreased physical function, frailty, and disability, HIV-infected persons typically experience physical performance impairment. Particularly in advanced HIV illnesses, these predisposing reasons may limit patients' daily activities and raise their risk of death (34). According to numerous studies, patients who do not follow their prescribed course of action are at a higher risk of dying than those who do. Patients who take their medication as prescribed will benefit the most from HAART, and their chances of survival are higher. Poor adherence is linked to an early treatment failure risk and a quick rise in drug resistance (40,41).

In this investigation, patients with TB were three times more likely to pass away than those without TB. This result is consistent with researches conducted in South Africa (42) and Iran (37), as well as a meta-analysis study at LMIC (33). This might be because people with HIV and TB who are also co-infected are more likely to acquire advanced AIDS stages quickly because their immune systems have been compromised. HIV and TB are cyclical diseases. Innovative measures to prevent TB infection should be put into practice, and TB preventive efforts should be scaled up to include routine INH distribution to all HIV-positive adults, rapid TB testing and diagnosis techniques, and urgent treatment (35, 37). According to this study, patients with significant anemia at the time of starting HAART were twice as likely to pass away from their HIV infection as those without anemia. This result is comparable to that from Tanzania (35), by which severe anemia was linked to increase incidence of death. Another study conducted at LMIC found that the risk of death was highest in anemic patients with hemoglobin levels below 8 g/dL (32). The best explanation for the data is that anemia among HIV-infected people is easily exposed to chronic diseases such as chronic heart failure that may be lethal to the patients (32,33).

5. Conclusion

In conclusion, early in the course of therapy, there was a high rate of mortality in this review and meta-analysis. Two-thirds of deaths occurred during the first year of follow-up after the start of HAART. The significant determinants identified in this review and meta-analysis that were associated with increased mortality included advanced WHO clinical stages III and IV, low CD4 cell count below 200 l/ml, low hemoglobin level, presence of TB co-infection, non-working functional status at the initiation of HAART. Routinely stepped-up HIV testing and counseling services, early HIV diagnosis, and prompt rapid HAART initiation for patients before their functional status deteriorates, their CD4 cell counts and/or they reached an advanced WHO clinical stage. All healthcare facilities offering ART service should also continue to monitor patients' adherence to their medication regimens and facility visit and provide health education on these topics. Strategies to lower TB infection should be put into practice, and TB preventive efforts should be scaled up to include routine INH distribution to all HIV-positive persons, quick TB screening, and prompt treatment by healthcare providers with proper health education on its significance in preventing opportunistic infections. The multisectoral response office and other parties involved in the HIV prevention and control program should place a priority on optimizing ART services and regularly update and retrain support staff and medical personnel. At every level of service supply, it's crucial to offer HIV-positive individuals a full range of medical treatment. It also provides guidance on how to avoid and control the HIV epidemic.
Since the studies that was included for the analysis was a retrospective cohort study; Patients who passed away at home without being recorded were assumed to be still living or unfollowable, which led to an underestimation of the mortality incidence. On the other hand, the actual cause of death was not consistently identified, which may have overestimated the rate of mortality. In a similar vein, individuals who died at a health facility and were registered in the ART registry were deemed to have died from HIV-related causes. Because there was no access to the databases, this review and analysis might not have included all of the relevant studies. For research purposes, only free databases (Pubmed, Google Scholar, Scopus, and DOAJ) have been accessed.

**Declarations**

**Protocol and Registration**

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement of 2020 (43). The protocol for this analysis was registered in the international prospective register of systematic reviews (PROSPERO), which can be accessed at http://www.crd.york.ac.uk/PROSPERO with the registration number of CRD42019123380.

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**Data access:** The included research data, the template used for data collection and the extraction procedure, and the data used for analysis can be obtained by contacting hablijalem2018@gmail.com.

**Contribution of the author**

Habtamu Lijalem: Started the investigation, drafted the research proposal, carried out the investigation, entered and analyzed the data, and authored the manuscript.

Shimelash Bitew: Started the investigation, drafted the proposal, carried it out, entered the data, performed the analysis, and prepared the report.

Amare Lisanu: Made a contribution to the proposal and manuscript writing.

Eshetu Hizkeal: Participated in the proposal and manuscript writing processes.

Muluken Gunta: Participated in the proposal and manuscript writing processes.

Amanuel Sisay: Participated in the analysis and manuscript writing processes. Everyone has contributed equally.

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**Tables**

Table 1 is available in the supplementary files section.

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PRISMA flow diagram showing the procedures of studies selection that were included in the final analysis.
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A forest plot showing the overall pooled estimate of incidence of mortality
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the result of sensitivity analysis among 21 studies conducted on adult HIV patients in Ethiopia
Figure 4

A forest plot of estimated hazard ratio of WHO staging on adult HIV patients in Ethiopia
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A forest plot showing the pooled hazard ratio of CD4 counts on adult HIV infected patients after HAART initiation in Ethiopia.
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Figure 7

A forest plot showing the pooled estimate of hazard ratio of patients with tuberculosis after HAART initiation in Ethiopia
Figure 8

A forest plot showing hazard ratio of patients with hemoglobin level at initiation of HAART in Ethiopia
Figure 9

A funnel plot assessing publication bias in the included studies.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- PRISMA2009checklistforadditionaldocument.doc