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Incidence density mortality rate among HIV-positive children on antiretroviral therapy in Ethiopia: a systematic review and meta-analysis.

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Abstract

Background Human Immunodeficiency Virus (HIV) continues to be the major cause of childhood deaths, particularly in the sub-Saharan African region. In Ethiopia, though several primary studies have been conducted on the incidence of HIV-related child mortality, the pooled incidence density mortality rate among HIV-positive children is unknown. Therefore, this systematic review and meta-analysis aimed to estimate the pooled incidence density mortality rate among HIV-positive children and identify its associated factors in Ethiopia.

Methods We browsed PubMed, HINARI, Science Direct, Google Scholar, African Journals Online, and cross-references using different search terms to identify articles. Quality appraisal was done using the Joanna Briggs Institute checklist. Meta-package was used to estimate the pooled incidence of mortality and hazard ratio (HR) of predictors. Heterogeneity was tested using the I-square statistics. Publication bias was tested using a funnel plot visual inspection and Egger's test. Data was presented using forest plots and tables. The random effect model was used to compute the pooled estimate.

Results The overall pooled incidence density mortality rate among HIV-positive children was 2.52 (95% CI: 1.82, 3.47) per 100 child years. Advanced HIV disease (hazard ratio (HR): 3.45, 95% CI (Confidence Interval): 2.64, 4.51), tuberculosis co-infection (HR: 3.19, 95% CI: 2.08, 4.88), stunting (3.22, 95% CI: 2.46, 4.22), underweight (HR: 2.71, 95% CI: 1.72, 4.26), wasting (HR: 4.14, 95% CI: 2.27, 7.58), didn't receive Isoniazid preventive therapy (HR: 3.33, 95% CI: 2.22, 4.99), anemia (HR: 3.03, 95% CI: 2.52, 3.64), fair or poor antiretroviral therapy adherence (HR: 4.14, 95% CI: 3.28, 5.28) and didn't receive cotrimoxazole preventive therapy (HR: 3.82, 95% CI: 2.49, 5.86) were factors associated with a higher hazard of HIV related child mortality.

Conclusions The overall pooled incidence density mortality rate among HIV-positive children was high in Ethiopia as compared to the national strategy target. Therefore, counseling on antiretroviral therapy adherence should be strengthened. Regular monitoring of hemoglobin levels and assessment of nutritional status should be done for all

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children living with HIV. Moreover, healthcare professionals should follow the national HIV treatment guidelines and provide cotrimoxazole preventive therapy and Isoniazid preventive therapy up on the guidelines for children living with HIV.

Registration Registered in PROSPERO with ID: CRD42023486902.

Keywords Incidence, Mortality, HIV, Children, Meta-analysis, Systemic review, Ethiopia

Background

Human Immunodeficiency Virus (HIV) is a virus that attacks the body's immune system, particularly the white blood cells called CD4 cells [1]. If HIV is not treated, it advances to Acquired Immune Deficiency Syndrome (AIDS) [2]. In this stage, people living with HIV have weak immunity and are highly susceptible to opportunistic infections [2, 3]. There is no cure for HIV, but antiretroviral therapy (ART) can reduce the morbidity and mortality of people living with HIV, mainly, by suppressing the viral load, improving the immune system, and reducing the risk of opportunistic infections [4]. Among the population group, infants and young children living with HIV are highly susceptible to opportunistic infections, if treatment is delayed [5].

Globally, an estimated 1.5 million children (aged 0–14 years) were living with HIV in 2022 [6–11]. The burden was higher in Sub-Saharan African countries where 87% of children(aged 0–14 years) living with HIV were contributed from this region [12, 13]. In Ethiopia, an estimated 33,026 HIV-positive children were projected for the year 2023 [14]. To reduce the burden of HIV, in 2015, the United Nations, under its Sustainable Development Goal (SDGS), set a global target to end the HIV epidemic By 2030 [15]. To achieve this target, an additional intermediate HIV prevention road map was endorsed for the years 2020 and 2025, setting a target to reduce the number of newly HIV-infected people to fewer than 500, 000 in the year 2020 and 370,000 in the year 2025 [16, 17]. However, the number of newly HIV-infected people continues to be unbeaten; globally, about 1.3 million people were newly infected with HIV in 2022, and of these, about 130,000 of them were children (aged 0–14 years) [6, 7, 18].

HIV continues to be a major childhood public health issue, in 2022, about 84,000 children (aged 0–14 years) died from HIV/AIDS-related causes globally [10, 13]. The African region holds about 70, 420 of the global HIV-related mortality among children (aged 0–14 years) in 2022 [12]. To halt HIV-related deaths, the United Nations has endorsed a 95-95-95 ambitious treatment target for the year 2025, which implies that 95% of people living with HIV know their status, 95% of people living with HIV who know their status are receiving treatment and 95% of people on treatment have suppressed viral loads by the year 2025 [19]. Despite progress made, the target lags for children that only 63%, 57%, and 46% of children (aged 0–14 years) knew their status, received ART, and was virally suppressed, respectively, globally in 2022 [12]. This indicates the need for a fast track to achieve the 2025 treatment target.

The incidence of death among HIV-positive children in Sub-Saharan Africa was 98.85 deaths per 1000 person-years [20]. Moreover, according to studies conducted in different African countries, the incidence of death among children living with HIV was 3.4 deaths per 100 child years in Malawi [21], 3.4 deaths per 100 child years in Democratic Republic of Congo [22], 3 deaths per 100 child-years in Nigeria [23], 8.4 deaths per 100 child-years in Kenya [24], 4.7 deaths per 100 child years in South Africa ([25] and 1.1 to 1.6 deaths per 100 child-years in Zambia [26, 27].

In Ethiopia, though the government has been working to reduce HIV-related deaths to less than 1 per 10,000 population by 2025 [28], the projected HIV-related mortality among children living with HIV remains high in Ethiopia [14]. According to studies conducted in Ethiopia, the incidence of mortality among children living with HIV raged from 1.5 per 100 child years [29] to 6.3 per 100 child years [30]. Moreover, several primary studies also confirmed that there was a considerable discrepancy in HIV-related child mortality across regions in Ethiopia, and different factors were associated with the mortality [29–49]. With this inconsistency, the pooled incidence density mortality rate among HIV-positive children has not been estimated in Ethiopia. Therefore, this systematic review and meta-analysis aimed to estimate the pooled incidence density mortality rate among HIV-positive children on ART and identify its associated factors in Ethiopia. The result of this study could help the policymakers, researchers, program implementers, and other responsible bodies by unveiling the burden of HIV related mortality and identifying its predictors among HIV positive children on ART.

Methods

Search strategy

The Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA) guideline was used to report the result [50]. PubMed, HINARI, Science Direct, Google Scholar, African Journals Online, and cross reference were browsed to obtain relevant studies. Searching was conducted from October 23, 2023 to back 10 years to provide an up-to-date pooled incidence density mortality rate among HIV-positive children on ART. The PECO term was used to formulate the research question (Additional Table 1) Based on this, the following terms and phrases such as" survival", "incidence rate", "mortality", "death", "treatment outcome", "predictors", "associated factors", "risk factors", "determinants", "pediatrics", "children" "under-five children", "newborn", "Human Immunodeficiency virus", "HIV"," Acquired Immunodeficiency syndrome", "ADIS", "ART", "antiretroviral therapy" and "Ethiopia" were used to search articles from the database. The Boolean search operators such as "AND" and "OR" were used separately and in combination during database searching (Additional Table 2)

Eligibility criteria

The inclusion criteria were: (1) studies conducted using cohort study design (2) studies that report the incidence of mortality rate among children (aged 0–14 years) living with HIV, studies that report the events (number HIV related deaths) among HIV-positive children, studies that report predictors using hazard ratio, (3) studies that report the child person-years or child months observation, (4) studies published in English languages and (5) studies available at the electronic source in the last 10 year to October 23, 2023 were included in the study. On the other hand, studies that report predictors other than hazard ratio and citations without full text were excluded from the analysis.

Data extraction

A total of 922 articles were exported to EndnoteX7 to identify and remove duplication. Four authors (GF, ZA, MS, and AA) independently extracted the data using a standardized data extraction form. From each study, the author's name, publication year, the event or number of deaths related to HIV, study region, study design, the total person year, incidence rate, follow-up time, and the predictor of mortality with hazard ratios were extracted.

Quality assessment/Critical appraisal

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort study design was used to assess the quality of the study [51]. The qualities of the primary studies were independently assessed by two authors (MG and AA). Any discrepancy between the two authors was handled by taking the mean score of the two authors. The tool has Yes, No, Unclear, and Not Applicable options: "1" is given for "Yes" and "0" is given for other options. The scores were summed and changed to percentages. Studies with >50% quality scores were included in this meta-analysis. Finally, 22 studies that received a quality score of >50% were included in this meta-analysis (Additional Table 3).

Outcome measurement

The first outcome of this systematic review and meta-analysis was the incidence density mortality rate among HIV-positive children in Ethiopia. The incidence density mortality rate among HIV-positive children was calculated by dividing the number of children who died by the total child follow-up year and multiplying it by 100. Identifying the factors associated with mortality among HIV-positive children was the second outcome of this study. Accordingly, the hazard ratio of predictors with its 95% confidence intervals (CI) was extracted from the original studies to compute the pooled hazard ratio.

Advanced HIV disease: children older than five years whose WHO clinical stages are III and IV. Whereas, children younger than five years living with HIV are considered as having advanced HIV disease, regardless of the clinical stages.

Mild WHO clinical stages: HIV-positive children whose WHO clinical stages are stages I and II [52].

CD4 count below threshold: CD4 counts less than 350 cells/mm^3 [52].

ART Adherence: **Good (>95%)**—if missed doses is ≤2 doses of 30 doses or ≤3 doses of 60 doses; **Fair: (85– 94%)** if missing doses is between 3 and 4 of 30 doses or 4–9 of 60 doses; **poor: (<85%)** if missed doses are >5 doses of 30 doses or 10 and above doses of 60 doses of ART drug [52].

Nutritional status: Underweight: (children with weight for age Z-score<−2 standard deviation (SD), **Stunting**: (height for age Z-score<−2 SD), **Wasting**: (weight for height Z-score<−2 SD) [53].

Statistical analysis

Data entry was done using Microsoft Excel Version 2013 and then imported into R software version 4.1.3 for further analysis. Meta-package was used to analyze the data. Heterogeneity was checked using the I-square [54]. Heterogeneity was declared as low, medium, and high if the I^2 value was 25%, 50%, and 75%, respectively [55]. Subgroup analysis was done based on the duration of follow-up time with evidence of heterogeneity. To identify the possible source of heterogeneity

meta-regression analysis was done considering the sample size and publication years. Sensitivity analyses were done by omitting individual studies to detect the contribution of each study to the final pooled incidence density mortality rate of HIV. Funnel plot visual inspection was done to identify publication bias. Finally, Egger's test was done to assess any significant publication bias. Further, trim and fill analyses were conducted to correct publication bias. Forest plots and tables were used to present the result. The random effect model was used to estimate the pooled incidence density mortality rate among HIV-positive children on ART.

Results

Characteristics of included studies

A total of 922 studies were searched from PubMed, HINARI, Science Direct, Google Scholar, African Journals Online, and cross-references. Of these, 145 studies were from PubMed, 348 studies were from HINARI, 363 studies were from Science Direct, and the rest 66 studies were browsed from Google Scholar, cross reference, and African Journals Online. From these studies, 152 studies were excluded due to duplication. From the remaining 770 articles, 712 studies were excluded as not being relevant to the study after reviewing the title and abstract. The rest 58 articles were browsed for full-text reviewing. Such that, a total of 36 studies were removed as they did not report the outcome interest (13 studies), focused on adults (22 studies), and we did not retrieve the full text (1 study). Finally, a total of 22 studies were eligible and incorporated in the final systematic review and meta-analysis [29–49, 56] (Fig. 1). All studies were conducted using cohort study design. These studies were done from different parts of Ethiopia (Addis Ababa city administration, Amhara regional state, Oromia regional state, SNNPR (South Nation, Nationalities and People Regional state), and Bnishangul Gumuz regional state, Tigray regional state, and Harari regional state) (Table 1)

The pooled incidence density mortality rate among HIV-positive children

In this meta-analysis, a total of 21 studies were used to estimate the pooled incidence density mortality rate among HIV-positive children on ART in Ethiopia [29–49]. Accordingly, the pooled incidence density mortality rate among HIV-positive children on ART in Ethiopia was 2.52 (95% CI: 1.82, 3.47) per 100 child-years observations using a random effect model. Heterogeneity ($I^2 = 94\%$, P-value < 0.01) was identified (Fig. 2) Sensitivity analysis was done to explore the contribution of each study for the final pooled estimate. Accordingly, except for one study [47], nearly all studies have equal contributions to the pooled incidence density mortality rate among HIV-positive children in Ethiopia (Fig. 3)

Subgroup analysis

Subgroup analysis was done based on the duration of follow-up time. Accordingly, the incidence density mortality rate among HIV-positive children was 2.24(95% CI: 1.37, 3.68) per 100 child years and 2.94 (95% CI: 2.02, 4.29) per 100 child years for children followed greater than 60 months and children followed less or equal to 60 months, respectively(Fig. 4)

Meta regressions

Meta-regression was the extension of subgroup analysis, which was conducted to identify the possible source heterogeneity using the publication years and sample size. Of these factors, none of them were statistically significant (Table 2)

Publication bias

Asymmetric distribution was identified in the funnel plot visual inspection (Fig. 5) The Egger's test also shows a statistically significant publication bias with B_0 = -1.97, p-value = 0.005. Due to the presence of statically significant publication bias, meta-trim and fill analysis were done. Hence, eight studies were filled and the incidence density mortality rate became 4.02 (95% CI: 2.71; 5.96) per 100 child years (Fig. 6).

Predictors of mortality among HIV-positive children in Ethiopia

A total of 21 studies were incorporated to estimate the pooled hazard ratio of factors associated with mortality among HIV-positive children on ART [29–31, 33–49, 56]. Accordingly, the hazard of mortality was 4.14 times (HR: 4.14, 95% CI: 3.28, 5.28) higher among children whose adherence level was fair or poor as compared to children with good ART adherence [29, 30, 36, 37, 41–44, 46–48, 56]. Children having a baseline CD4 count below the threshold were 2.6 times (HR: 2.6, 95% CI: 2.08, 3.27) more likely to die as compared to children having a CD4 count above the threshold [29, 31, 33–35, 37–40, 42, 45]. The likelihood of mortality was 3.82 times (HR: 3.82, 95% CI: 2.49, 5.86) higher among children who didn't receive CPT as compared to children who received CPT [34, 39, 44, 45]. The hazard of mortality was 3.03 times (HR: 3.03, 95% CI: 2.52, 3.64) higher among children who have low hemoglobin levels as compared to children who have normal hemoglobin levels [29, 31, 35–42, 44–49]. The likelihood of mortality was 3.33 times (HR: 3.33, 95% CI: 2.22, 4.99) higher among children who didn't receive IPT as compared to children who received IPT

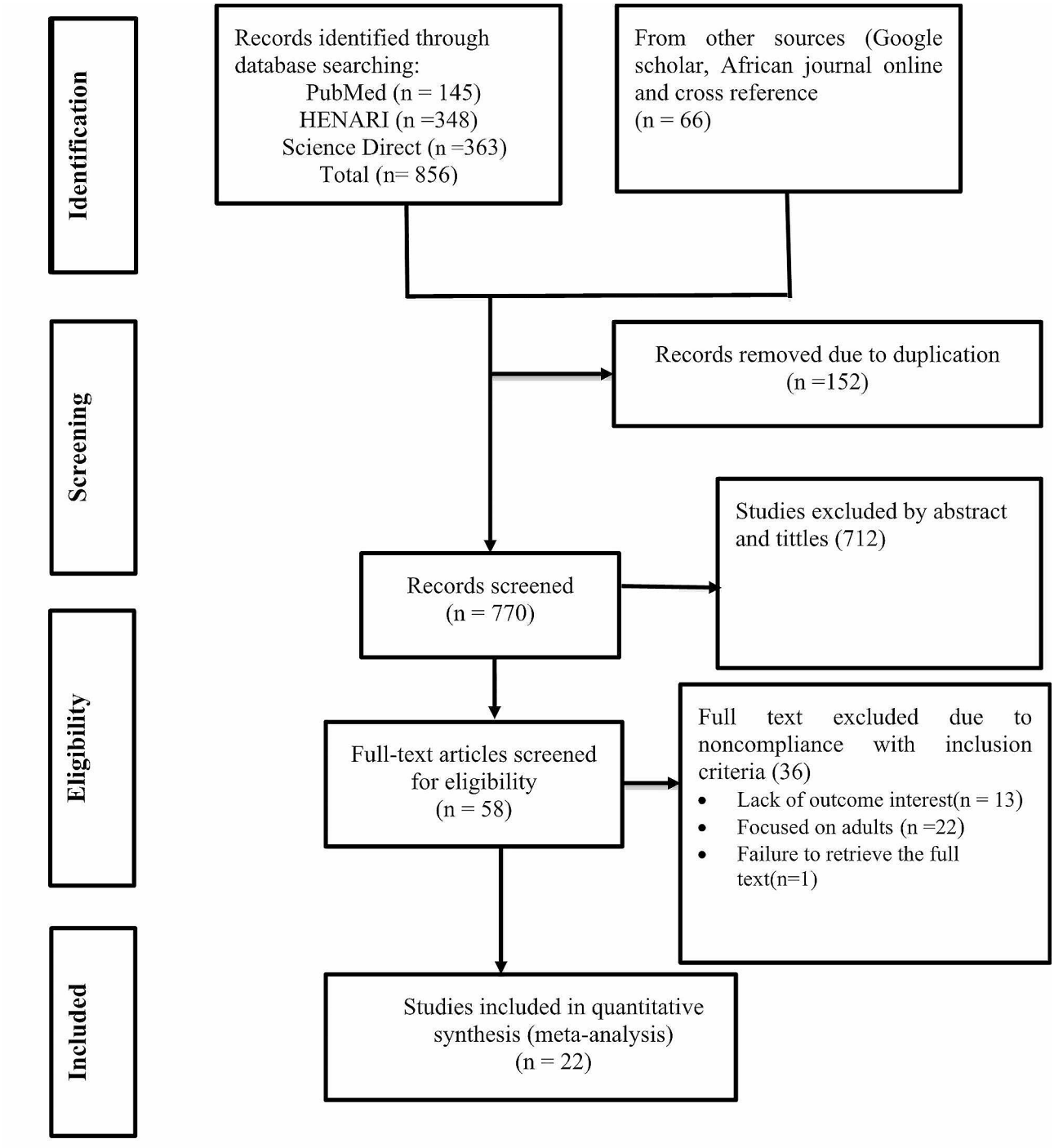

Fig. 1 PRISMA flow chart describing screening protocols of studies for Meta-analysis

[36, 44, 47, 48, 56]. The hazard of HIV-related mortality was 3.19 times (HR: 3.19, 95% CI: 2.08, 4.88) higher among children who were co-infected by tuberculosis as compared to their counterparts [37, 42, 49].

The hazard of child mortality was 3.22 times (HR: 3.22, 95% CI: 2.46, 4.22) higher among children who were stunted as compared to their counterparts [29, 33, 38]. The likelihood of mortality was 2.71 times (HR: 2.71, 95% CI: 1.72, 4.26) higher among children who were underweight as compared to their counterparts [35, 46, 49]. The risk of mortality was 4.14 times (HR: 4.14, 95% CI: 2.27, 7.58) higher among children who were wasted as compared to their counterparts [29, 38, 43, 45]. The risk of child mortality was 3.45

Table 1 Characteristics of studies included in the meta-analysis for the pooled incidence density mortality rate among HIV-positive children, Ethiopia, 2023

Author	Region	sample sizes	Number of death	Follow-up time	PYO	PMO	IDMR per child years	IDMR per child months
Mulgeta et al. (2017) [31]	Addis Ababa	757	51	83	4112		12.4 per 1000	
Edessa et al. (2015) [32]	Harari	305	28	30	609	7, 312	--	3.8 per 1000
Molla et al. (2022) [33]	Benishangul-Gumuz	721	90	36.86	1676.4	20116.85	5.4 per 100	--
chanie et al. (2018) [34]	Amhara	227	39	167	1063.17	12,758	3.7 per 100	--
Adem et al. (2014) [35]	Oromia	560	43	62	2078	--	2.06per 100	--
Dawit et al. (2021) [36]	SNNPR	274	47	96	1581.3	--	2.97 per 100	--
Sidamo et al. (2017) [37]	SNNPR	421	65	95	1764.58	21,175	--	3.07 per 1000
Haile et al(2021) [29]	SNNPR	429	39	140	2549.6	--	1.5 per 100	--
Alebel et al. (2020) [38]	Amhara	538	38	39	1216	14,600	3.2per 100	--
Koye et al. (2012) [39]	Amhara	549	41	62	1025	--	4 per 100	--
Gebremedihn et al. (2013) [40]	Tigray	416	20	50	1186.25	14,235	16.85 per 1000	1.4 per 1000
Gemech et al. (2022) [41]	SNNPR	284	35	120	1257.17	--	2.78 per 100	--
Tagesse et al. (2020) [42]	Addis Ababa	410	22	44	1103	--	19.9 per 1000	--
Bitew et al. (2017) [43]	SNNPR	228	16	97	760.95	9131.4	21.02 per 1000	--
Atallel et al. (2018) [44]	Amhara	271	38	78	1167.67	--	3.27per 100	--
Biyazin et al. (2022) [45]	Amhara	251	16	60	626	--	2.56 per 100	--
Arage et al. (2019) [30]	Amhara	426	97	120	1548.58	18,583	6.3 per 100	52.2 per 10,000
Chekole et al. (2022) [46]	Amhara	588	27	51	2505	30062.3	2 per 100	0.9 per 1000
seid et al. (2023) [47]	SNNPR	261	18	144	9477.5	18,955	1.9 per 1000	1.05 per 1000
Alemu et al(2022) [48]	Amhara	415	25	48	725.04	8700.5	3.45 per100	2.87 per 1000
Mekonen et al. (2022) [49]	Addis Ababa	415	41	56	686.4	8237	5.97 per 100	4.98 per 1000
Woldemariam et al. (2022) [56]	Amhara	376	21	41	--	--	5.9 per 100	--

IDMR: incidence density mortality rate, PYO: Person-year observation, PMO: Person-month observation

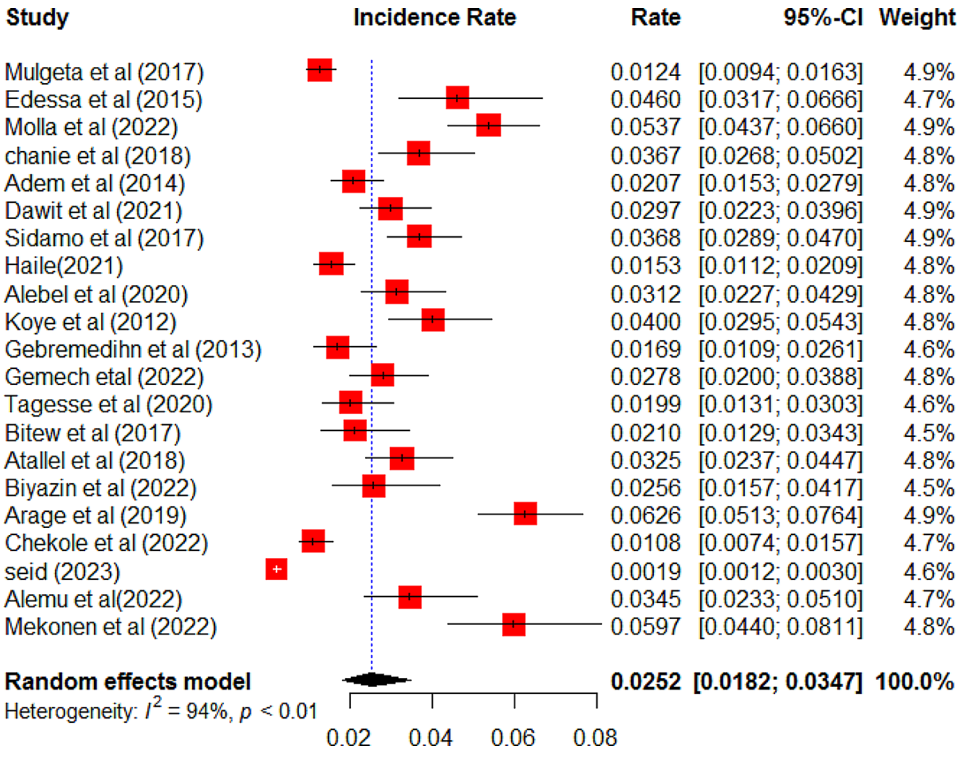

Fig. 2 The forest plots shows the incidence density mortality rate among HIV-positive children, Ethiopia, 2023

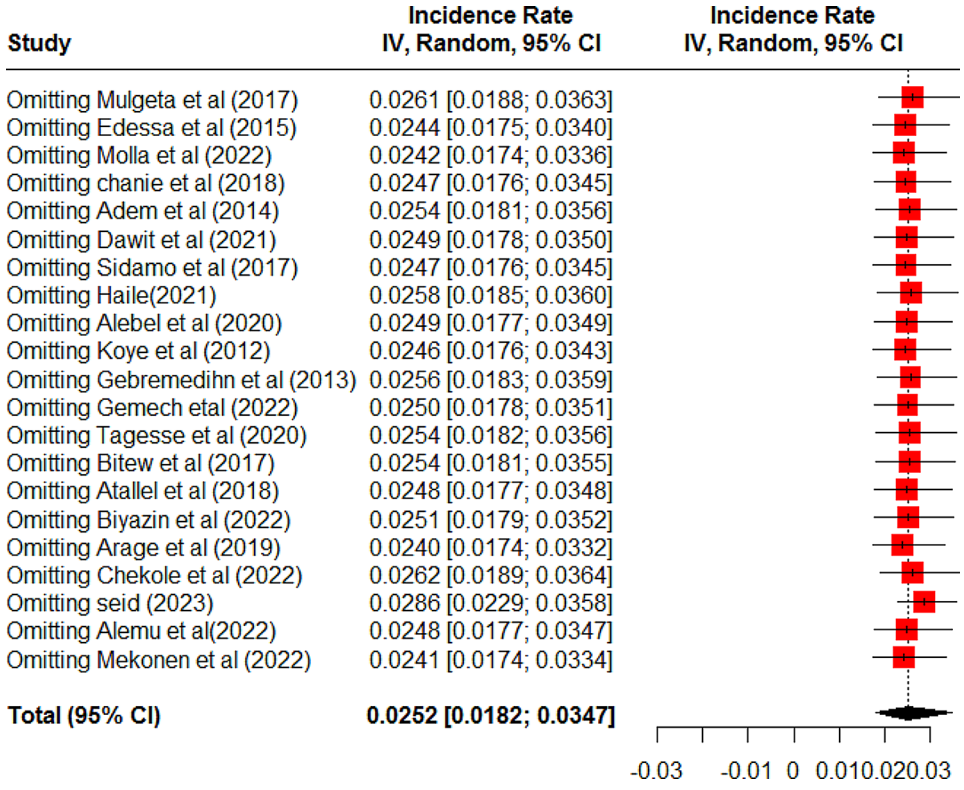

Fig. 3 Sensitivity analysis for the incidence density mortality rate among HIV positive children in Ethiopia

times (HR: 3.45, 95% CI: 2.64, 4.51) higher among children with advanced HIV disease as compared to children with mild WHO clinical stages [29, 31, 33, 35, 38, 40, 42, 46, 49, 56] (Table 3).

Discussion

In Ethiopia, though there are several fragmented studies on the incidence of mortality among children living with HIV, the aggregated incidence density mortality rate among HIV-positive children has not been investigated. Therefore, this systematic review and meta-analysis aimed to disclose the pooled incidence density mortality rate among HIV-positive children on ART and further, explore the factors associated with it. Accordingly, the pooled incidence density mortality rate among HIV-positive children on ART was found to be 2.52 (95% CI: 1.82, 3.47) per 100-child-year observations. The finding is high and requires a fast track to achieve the national HIV/AIDS mortality reduction target of 1 per 10,000 population by the year 2025 [28]. The possible justification for the high mortality rate might be due to economic constraints to implement the strategies related to HIV. This is the fact that the 95-95-95 strategic target lags for children (aged 0–14 years) living with HIV [12].

The risk of death is higher among children who have fair or poor adherence levels as compared to children who have good ART adherence levels. The finding is supported by studies conducted elsewhere [57, 58]. This is the fact that ART can halt viral replication and boost the immune function and it prevents opportunistic infection [59, 60]. Such that, fair or poor ART adherence can open a window for viral replication. This can increase the risk of HIV-related deaths.

This systematic review and meta-analysis revealed that children having baseline CD4 counts below the threshold are more likely to die as compared to those having a CD4 count above the threshold. The finding is congruent with studies conducted elsewhere [22, 25, 58, 61–66]. This is the fact that CD4 cells are crucial for regulating the immune response to pathogens, and their proper functioning is important for survival [67]. Such that, low CD4 count increases the vulnerability to opportunistic infection, which later causes child morbidities and mortalities.

The likelihood of mortality is higher among children who didn't receive CPT as compared to children who received CPT. The finding is supported by the previous study conducted in South Africa [66]. This is the fact that cotrimoxazole blocks the biosynthesis of nucleic acid and protein which is crucial to many opportunistic infections [68]. Thus, CPT can reduce the risk of acquiring opportunistic infection among children living with HIV.

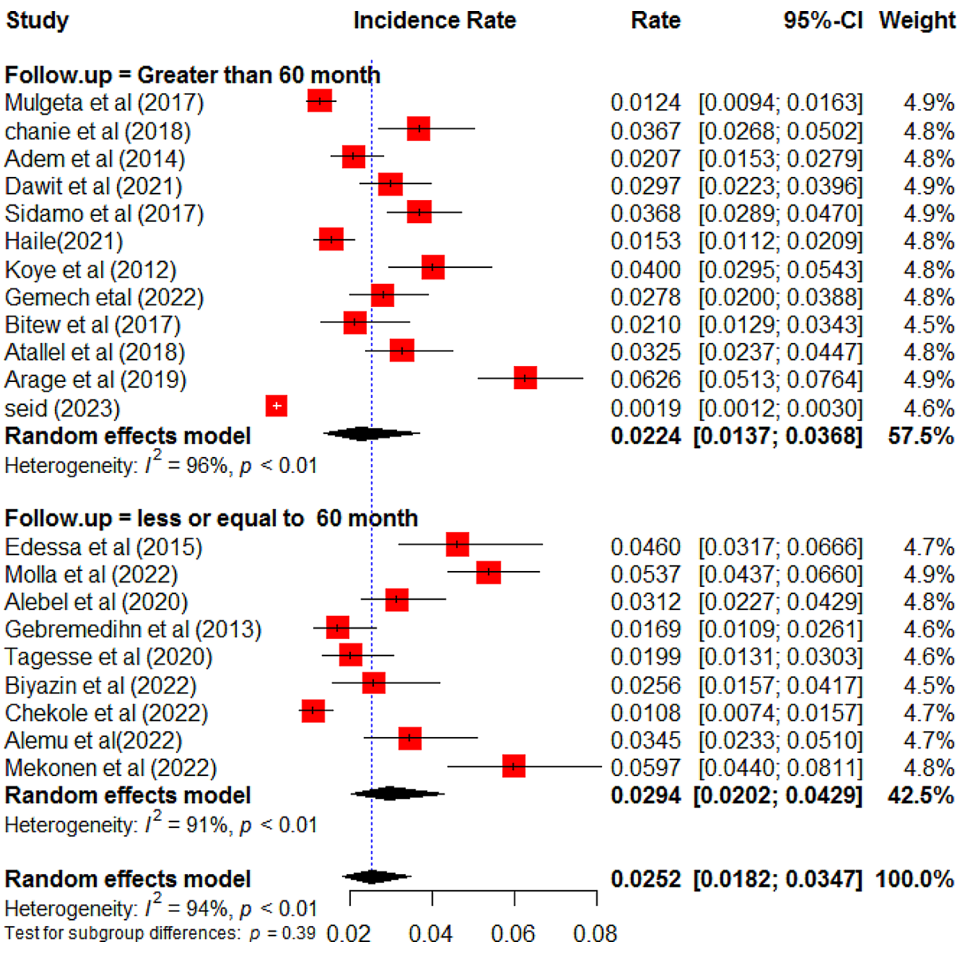

Fig. 4 Forest plot shows the subgroup analysis of the incidence density mortality rate among HIV-positive children by duration of follow-up period

Table 2 Meta-regression analysis using publication years and sample sizes for the possible source of heterogeneity of incidence density mortality rate among HIV-positive children, Ethiopia, 2023

Variables	Coefficients	*P*-value
Publication years	-0.0405 (-0.1412, 0.0603)	0.4
Sample size	0.0002 (-0.0019,0.0024)	0.83

This systematic review and meta-analysis discovered that the hazard of mortality is higher among children who have low hemoglobin levels as compared to children who have normal hemoglobin levels. The finding is consistent with studies conducted elsewhere [24, 69–72]. This could be the fact that anemia can impair the body's immune function [73–76]. Thus, it synergizes the progression of HIV to the advanced stage and can cause premature death.

The likelihood of mortality is higher among children who didn't receive IPT as compared to children who received IPT. The finding is congruent with the previous studies conducted elsewhere [77, 78]. This could be the fact that IPT can reduce the incidence of opportunistic infection, particularly tuberculosis disease among HIV-positive patients [79–82]. Thus, children who didn't receive IPT have a higher risk of acquiring opportunistic infection. This can increase the risk of HIV-related mortality.

In this meta-analysis, malnourished children have a higher hazard of HIV-related mortality as compared to normally nourished children. The finding is supported by studies conducted elsewhere [20, 21, 25, 61, 64, 70]. This is the fact that micro and macronutrients are needed to boost the body's immunity system [75]. Thus, being malnourished is a golden opportunity for viral replication, which further compromises the body's immune system. This can increase the risk of mortality.

This systematic review and meta-analysis also revealed that the risk of child mortality is higher among children with advanced HIV disease as compared to children with mild WHO clinical stages. The finding is synonyms with studies conducted elsewhere [20, 27, 64, 66, 70, 71, 83–85]. This could be the fact that children with advanced HIV stage have compromised body immune systems and are more susceptible

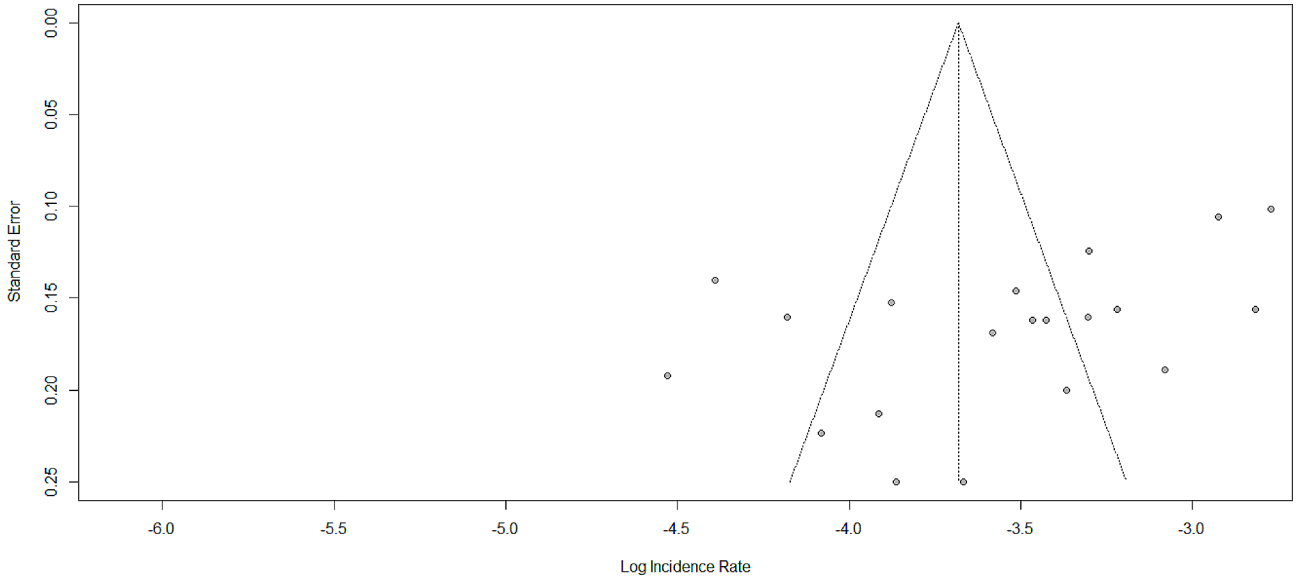

Fig. 5 Funnel plot showing publication bias among studies used to compute the pooled incidence density mortality rate among HIV positive children, Ethiopia

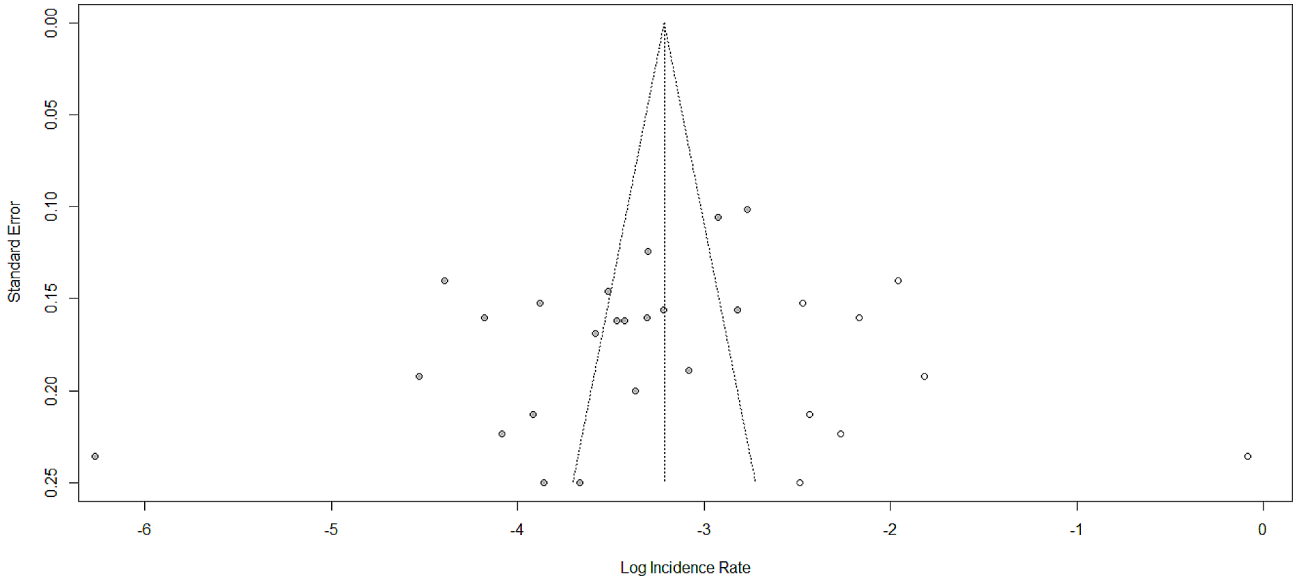

Fig. 6 Shows the trim fill analysis for the incidence density mortality rate among HIV positive children, Ethiopia, 2023

to opportunistic infections, which exacerbates the risk of mortality.

Lastly, this systematic review and meta-analysis revealed that the hazard of HIV-related mortality is higher among children who are co-infected by tuberculosis as compared to their counterparts. The finding is consistent with previous studies conducted elsewhere [20, 83]. This could be the fact that tuberculosis has a synergistic effect on the progression of HIV/AIDS. Thus tuberculosis coinfection can exacerbate the impairment of the body's immune system.

The clinical and public health implications of this systematic review and meta-analysis are to take prompt intervention against the identified factors and response to reduce the burden of HIV-related mortality. Therefore, researchers, program implementers, and policymakers should consider the aforementioned factors in their preventive strategic plan.

Limitation

This systematic review and meta-analysis have the following limitations, (1) In this analysis, articles published only in English were included, (2) only seven

Table 3 Predictors of mortality among HIV-positive children in Ethiopia, 2023

Variables	Number of studies	Pooled HR (95% CI)	Heterogeneity
Poor or fair ART adherence	12	4.14(3.28, 5.28)	(I^2 = 0, *P*-value = 0.5)
CD4 count below threshold	11	2.60(2.08, 3.27)	(I^2 = 0, *P*-value = 91)
Didn't receive CPT	4	3.82(2.49, 5.86)	(I^2 = 0, *P*-value = 0.79)
Anemia	16	3.03 (2.52, 3.64)	(I^2 = 0, *P*-value = 0.1)
Didn't receive IPT	5	3.33(2.22, 4.99)	(I^2 = 0, *P*-value = 0.94
Tuberculosis coinfection	3	3.19(2.08, 4.88)	(I^2 = 15%, *P*-value = 0.31)
Underweight	3	2.71(1.72, 4.26)	(I^2 = 0, *P*-value = 0.88)
Stunting	3	3.22 (2.46, 4.22)	(I^2 = 0, *P*-value = 0.67)
Wasting	4	4.14 (2.27, 7.58)	(I^2 = 0, *P*-value = 0.81)
Advanced HIV disease	10	3.45(2.64, 4.51)	(I^2 = 0, *P*-value = 0.92)

References: Poor or fair ART adherence vs. good ART adherence, CD4 count below threshold Vs above threshold, Didn't receive CPT Vs received CPT, Tuberculosis coinfection vs. no Tuberculosis coinfection, Underweight vs. normal, Stunting vs. normal, Wasting vs. normal, Advanced HIV disease Vs Mild WHO clinical stages

HR: Hazard Ratio, CI: Confidence Interval

regions were included in the analysis, thus, some regions may not be represented, (3) some variables associated with mortality among HIV positive children were excluded from the analysis because of there were reported only in one primary article and/or categorized differently from the included articles and (4) in this study, all the primary studies used to estimate the pooled incidence of mortality rate were conducted among HIV positive children on ART, thus, the incidence of mortality rate reported in this study may not represent children who didn't receive ART treatment.

Conclusion

The overall pooled incidence density mortality rate among HIV-positive children was high in Ethiopia as compared to the national strategy target. Advanced HIV disease, low CD4 count, tuberculosis co-infection, stunting, underweight, wasting, didn't receive IPT, anemia, fair or poor antiretroviral therapy adherence, and didn't receive CPT are identified as factors associated with mortality among HIV-positive children. Therefore, counseling on ART drug adherence should be strengthened. Regular monitoring of hemoglobin levels and assessment of nutritional status should be done for all children living with HIV. Full clinical assessments have to be done for all children living with HIV and the respective clinical stages should be documented in each follow-up. Up on this, special emphasis has to be given to children with advanced HIV disease and low CD4 count. Moreover, children living with HIV should be screened for tuberculosis co-infection and other opportunistic infections during follow-up. Lastly, healthcare professionals should follow the national HIV treatment guidelines and provide cotrimoxazole preventive therapy and Isoniazid preventive therapy up on the guidelines for children living with HIV.

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral treatment
CI	Confidence interval
CPT	Cotrimoxazoles preventive therapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
IPT	Isoniazid preventive therapy
JBI	The Joanna Briggs Institute Critical Appraisal Checklist
PMO	Person-month observation
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis Statement
PYO	Person-year observation
SNNPR	South Nation Nationalities and People Region
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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DG, GF ZA, MS, AA, AA, and MG are involved in the design, selection of articles, data extraction, quality appraisal, and statistical analysis. DG and GF were involved in manuscript writing. All authors read and approved the final draft of the manuscript.

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Data availability

The data is available at the corresponding author and can be provided upon request.

Declarations

Ethics approval

Not applicable.

Consent for publication

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Competing interests

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