Mortality and its Predictors among children on Antiretroviral treatment in Ethiopia: A systematic review and Meta – analysis

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Abstract

Background: It is well known that antiretroviral therapy (ART) decrease the progress of acquired immune deficiency syndrome (AIDS) related morbidity and mortality and helps the progress towards achieving the United Nations Program on HIV/ AIDS(UNAIDS) treatment goals. Despite this, mortality in Ethiopia becomes public health concern, and variance is observed across studies. With this gap, there is no pooled estimate. Thus, the goal of this study was to assess the pooled mortality and its predictors among antiretroviral treated HIV/AIDS patients.

Methods: PubMed, Scopus and Google Scholar databases were used to search articles. The quality of studies was assessed using the Newcastle Ottawa quality assessment scale. The funnel plot and Egger's test were performed to confirm the presence of publication bias. Heterogeneity across studies was evaluated using the I^2 statistic. The pooled incidence rate and its predictors were estimated using a weighted inverse variance random-effects model. Subgroup analysis and sensitivity analysis were also performed.

Results: In this review, 12 studies with the cohort size of 4,935 were included. The overall incidence of mortality rate was 6.02 (95% CI: 3.7, 8.2) per 100 person-years. A higher incidence of mortality was observed (12.51% (95%CI: 0.32, 24.7)) in south nation nationality and Peoples (SNNP) on subgroup analysis. Being advanced world health organization(WHO) clinical stage (AHR:5.34(95% CI: 3.1,9.2.6)), lower CD4 cell count (AHR :2.46 (95 %CI: 1.8, 3.2)), anemia (AHR :2.76 (95% CI: 1.9,3.9)), and nutritional status (AHR :1.9 (95%CI: 1.3, 2.6)) were major predictors of mortality. In contrast, cotrimoxazole preventive therapy (CPT) (AHR: 0.34, (95% CI 0.05, 0.63)) reduced mortality.

Conclusions: In Ethiopia, the incidence of mortality was high. Lower CD4 cell count, anemia, WHO clinical staging (III/IV), and undernutrition were the contributing factors. But cotrimoxazole preventive therapy had a high effect on mortality reduction. Therefore, an earlier management would be started before advancing signs of acquired immune deficiency syndrome (AIDS) regardless of WHO staging, CD4 cell level, and nutritional status.

Background

The pandemic of Human Immunodeficiency Virus (HIV)/ Acquired immune deficiency syndrome (AIDS) continues to take a tremendous toll on human health, having claimed more than 36.7 million peoples were affected worldwide. Of whom, 1.8 million were children (1). It progresses very rapidly among infants and children. In the absence of Antiretroviral Therapy(ART), 33 % of infants will die before their first birthday, and 50 % will die before the age of two years (2).

Sub-Saharan Africa is the most affected region, with 25.6 million people living with HIV(PLHIV) and accounts for two-thirds of the global total newly infected(1). Near to 91% of HIV positive children are also in this region (3). HIV /AIDS) remains the foremost reason for death in children (4).

Highly Active Antiretroviral Therapy (HAART) increases the survival and quality of life of people living with HIV/ AIDS (5). It is targeted to improve the immune system and maximize durable suppression of viral reproduction, restoring immunologic function, reduction of HIV/AIDS-related illness and death, improving the quality of life, and extending survival(1).

The World Health Organization (WHO) targeted to reach 15 million ART users by the end of 2015 and reached ahead of schedule. Nevertheless, still, 20 million HIV positive were not able to access ART (6). Moreover, access to ART is still low for children (7). Different studies conducted in developed (8, 9) and developing countries showed that inconsistency and increase mortality in children despite the availability of ART (10, 11).

Ethiopia is categorized among one of the sub-Saharan countries with the highest HIV/ADIS burden, with about 1.1 million were infected with 14,405 new infections per year. From this, approximately 109,133 were Children's which accounts for 2,420 of the newly infected(12). The government launched fee-based ART in 2003 and free-based in 2005, delivered as part

of the comprehensive HIV/AIDS care (13). Despite the rapid scale-up of children ART coverage, it is still very low in Ethiopia (14).

Multi-factorial causes contribute to increasing the burden of mortality in antiretroviral treated HIV/AIDS -Positive children. However, some major risk factors include low hemoglobin count(<10g/dl) (5, 15), low CD4 count or % below the threshold level (5), WHO clinical stage(III&IV) (5, 15), poor adherence to ART (16), and severe wasting (17). In our country, several single institution-based studies have been conducted in different regions. But, the incidence of mortality varied largely across studies which range from 4.02% (18)to 22.9%(19).

The level of mortality among children on ART in Ethiopia represented with high inconsistency and variable figures. For instance a study in Amhara region for example showed that the proportion of mortality ranges from 7.7-22.9% (18-20) and 10-15.5% in SNNPR region(21-23).with this discrepancy there is no any pooled result. Therefore, this study aimed to estimate the pooled incidence of mortality and its predictors in antiretroviral treated HIV/AIDS -positive children in Ethiopia. Therefore, this study aimed to estimate the pooled incidence of mortality and its predictors in antiretroviral treated HIV/AIDS -positive children in Ethiopia.

Methods

Literature search strategy

PubMed, Google Scholar, Scopus, and Web of Science databases were used to get the articles. Grey literature, such as unpublished articles and conference abstracts, were assessed. Endnote X 8.1 reference manager software was used to gather the searched articles and for the removal of duplicate articles. The search was conducted using the following terms and phrases: "Human Immunodeficiency virus", "Acquired Immunodeficiency syndrome", "antiretroviral therapy", "AIDS", the incidence of mortality "HIV", "predictors", "determinates" "children" and "Ethiopia". The searching date in PubMed through search terms was 26/04/2020. The search strategy made in PubMed was: (((("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND Predictors[All Fields]) AND (("anti-retroviral agents"[All Fields] OR "anti-retroviral agents"[MeSH Terms] OR ("anti-retroviral"[All Fields] AND "agents"[All Fields]) OR "anti-retroviral agents"[All Fields] OR "antiretroviral"[All Fields]) AND treated[All Fields] AND ("acquired immunodeficiency syndrome"[MeSH Terms] OR ("acquired"[All Fields] AND "immunodeficiency"[All Fields] AND "syndrome"[All Fields]) OR "acquired immunodeficiency syndrome"[All Fields] OR "hiv aids"[All Fields]) AND -Positive[All Fields])) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])) AND ("ethiopia"[MeSH Terms] OR "ethiopia"[All Fields]) Additionally, articles were searched from Addis Ababa University electronic repository system.

Inclusion and exclusion criteria

Articles were included if they fulfill the following standards: (1) HIV/AIDS infected children whose age is below 15 years old and on ART. (2) Observational studies like cohort, case-control, and cross-sectional studies, (3) studies that report the incidence rate, prevalence and/ or HR (hazard ratio), OR (odds ratio) of Predictors in Antiretroviral treated HIV/AIDS –Positive children, (4) studies done in Ethiopia, and [4] studies published in English language . Studies that didn't report the incidence/prevalence and/or determinants of mortality. Studies conducted on adult HIV infected patients or included both adults and Studies that will not provide full information/ missed data were excluded.

Studies conducted on adult HIV infected patients or included both adults and children and Studies that will not provide full information/ missed data were excluded.

Outcome measurement

The primary outcome is the level of mortality and the secondary outcome is major predictors in Antiretroviral treated HIV/AIDS -positive children.

Operational definitions

Incidence of mortality: The rate of child death during the follow-up period to the total person-years of observation.

WHO clinical stage: categorized as exposed when they are in advanced WHO clinical staging (stage three and four) and non-exposed (stage one and two)

Low CD4 count: it was classified based on the child's age (for Infants $CD4 < 1500/mm^3$, 12–35 months $< 750/mm^3$, 36–59 months $< 350/mm^3$ and ≥ 5 years $< 200/mm^3$)⁽²⁴⁾

Anemia: was defined and graded according to age-appropriate reference standards published by WHO ⁽²⁵⁾ and the report of included studies (Anemia was defined as having hemoglobin level of less than 10 mg/dl.

Nutritional status: malnourished /undernutrition was defined as weight for age Z-score < -2 SD for under-five children and BMI for age Z-score < -2 SD for older children

Methods for Data Extraction and Quality Assessment.

We used a Microsoft excel form to extract data. The following information was extracted for each incorporated finding: the name of the first author, publication year, country, region, study design, associated factors, sample size, final included, response rate, study settings, risk estimate (HR), incidence rate and the 95% confidence interval. Data extraction from source documents was done independently by all investigators. Disagreements were resolved by consensus. The quality of the included studies was evaluated using the Newcastle–Ottawa Scale (NOS) ⁽²⁶⁾. The criteria for cohort studies were selection graded by six stars, comparability graded by two stars, and outcome graded by five stars. Cohort studies scored 9 and/or above quality assessment criteria were included.

Data synthesis and statistical analysis

STATA 14 statistical software was used for analysis. Publication bias was assessed by the funnel plot and Egger's regression test. I^2 statistics were used to check the heterogeneity of studies. The DerSimonianLaird random-effects model was done to estimate the overall level. Subgroup analysis based on the region of the studies was conducted. Sensitivity analysis was also conducted to see the effect of a single study on the overall effect estimation.

Results

Explanation for original studies

A total of 473 articles were retrieved from PubMed (n=186), Google Scholar (n=244), Web of Science (n=8), Scopus (n=18), and Addis Ababa University's' online source library (n=1) and 16 in other sources. A total of 326 articles have remained after duplicate studies were removed. Of which, 126 were rejected just by reading only the titles. Of the remaining 90 studies, 51 were excluded after reading their abstracts. Full text copies of the remaining 39 studies that potentially fulfilled the inclusion criteria were assessed. After further screening, 12 papers were retained for inclusion, and all were published in the English language. Based on the predefined criteria and quality assessment, only 12 articles were included for the final analysis (Figure1).

Characteristics of the included studies

In this systematic review and meta-analysis, 12 studies with the cohort size of 4,935 pediatric patients on ART were included. Searches from the databases were done between 2012 and 2018. All of the studies which were included in this review had a

cohort study design. Three of the studies were conducted in the Amhara region(18-20) and the other three of the studies were conducted in SNNPR region(21-23), while two in Addis Ababa (16, 27)and Oromia(28, 29), one in Tigray(30) and one in Harari(31). The sample size of the studies ranging from 96 (28) to 757(27)(table 1).

Table 1: Characteristics of the included studies

ar	Area	Region	Total sample	Incidence of mortality	Response Rate	Media follow up
et al/2015	Harer	Harari	305	3.8	100	30
/2012	Bahir Dar	Amhara	579	4	94.81	22
hlin et al./2013	Mekelle	Tigray	432	1.4	96.3	36
l. et al/2009	Jimma	Oromia	96	2.1	100	24
il./2018	Debre Tabor	Amhara	462	5.2	92.2	44
al./2018	Arba Minch	SNNP	421	15.3	100	41
l./2014	Adama	Oromia	560	2.06	100	47
/2017	Addis Ababa	Addis Ababa	757	12.4	100	9
et al./2015	Addis Ababa	Addis Ababa	556	3.5	100	-
et al./2016	Jinka	SNNP	350	1.75	100	-
l./2017	Wolaita	SNNP	260	21.02	87.6	-
l2018	Gondar	Amhara	271	3.27	100	4

Publication bias and heterogeneity

The presence of heterogeneity and publication bias was evaluated within included studies. Subsequently, there was no any significant heterogeneity across the included studies in this meta-analysis ($I^2 = 44.2\%$). We found that there was publication bias among the included studies, as depicted by the asymmetrical distribution of our funnel plot (Figure 2). Likewise, the result of Egger's test was statistically significant for the presence of publication bias ($P = 0.004$). To reduce and adjust publication bias, trim and fill analysis was also performed(figure 4).

Mortality among children on Antiretroviral treatment

The current meta-analysis using the random-effects model showed that the estimated overall incidence of mortality in antiretroviral treated HIV/AIDS -Positive Children was 6.02 (95% CI: 3.7, 8.2) per 100 person-years of observation with the low level of heterogeneity ($I^2 = 44.2\%$, $p = 0.64\%$) (Figure 3).

A total of 9.2 % (95%CI: 6.8, 11.53) was died during the follow-up time (Table 2).

Table 2: the proportion of mortality in antiretroviral treated HIV/AIDS -Positive Children

Author/year	Proportion (95% CI)	Weight (%)
Dumessa et al (2015)	9.2 (5.9, 12.4)	8.15
Koye et al (2012)	7.5 (5.3, 9.7)	8.90
Gebremedhin et al. (2013)	4.81(2.75, 6.8)	9.0
etsanet W. et al (2009)	7.3 (2.1, 12.5)	6.53
Arage et al. (2018)	22.9 (18.9,26.9)	7.54
Sidamo et al. (2018)	15.4(11.9, 18.8)	7.9
Kedir et al., (2014)	7.6(5.4, 9.8)	8.91
Dube et al. (2017)	6.7 (4.9,8.5)	9.2
G. Ebissa et al. (2015)	10.4(7.9, 12.9)	8.7
Tachbele et al. (2016)	10 (6.9, 13.1)	8.2
Bitew et al. (2017)	6.8(3.5, 10.1)	8.13
Atalel et al. (2018)	4.02 (1.7, 6.4)	8.8
Pooled estimate	9.2(6.8,11.53)	9.2

Subgroup analysis

Subgroup analysis was employed based on region and sample size of the study participants, study design. A higher incidence of HIV/AIDS-related mortality was 12.51% in SNNP (95%CI: 0.32, 24.7). But there is no any difference in mortality with sample size (Table 3).

Table 3: Subgroup analysis with the region and sample size of the study participants

Subgroup analysis	Category	The pooled incidence of mortality (95%CI)	% Weight	p-value	Heterogeneity (I ²)
Sample size	<400	5.54 (1.91 ,9.17)	39.78	0.32	38
	>400	5.99(3.18 ,8.82)	60.22	0.64	5.39
Region	Addis Ababa	7.9 (0.81, 16.6)	17.25	0.34	67.8
	Amhara	4.131 (3.03, 5.23)	25.9	0.439	0.0
	SNNP	12.51(0.32, 24.7)	22.28	0.61	65.1
	Oromia	2.16 (0.97, 3.15)	17.01	0.98	97
	Tigray	1.4(0.27, 2.5)	9.1	0.00	-
	Hareri	3.8(1.65, 5.9)	8.5	0.001	-

Meta-regression

To examine the likely causes of disparity across studies, we conduct meta-regression analysis using publication year and sample size. But the result showed there is no any significant heterogeneity (Table 4).

Table 4: Meta-regression results of the included studies.

	Coefficient	Standard error	T	P-value	95% CI
Publication year	1.19.	0.68	1.74	0.12	0.35, 2.73
Total sample size	0.001	0.011	0.17	0.87	0.02 0.02

Trim and fill (figure 4)

Sensitivity analysis

Sensitivity analysis indicated that the impact of each finding on pooled estimate was insignificant, telling the robustness of aggregated estimate. Hence, the pooled mortality among HIV infected children on ART was constant and unaffected when assessed by removing one study at a time which implies no any single study significantly affect the pooled mortality result of the current meta-analysis (figure 5).

Predictors of Mortalities

WHO clinical staging

In this review pooled effect of six studies showed being on WHO clinical stage III/ IV found to be at higher risk (AHR=5.346; 95% CI: 3.1–9.2.6) to death as compared to stage II/I. Having a Progressive WHO staging (stage III and IV) at the baseline was 5.36 times more likely to die than the WHO clinical stage I and II (figure 6).

Baseline CD4 Cells count

Baseline CD4 Cells count was also another contributing factor to the incidence of mortality in antiretroviral treated HIV/AIDS -positive children. The pooled hazard ratio of patients with low CD4 cell count at the initiation of HAART was 2.46 (95 %CI: 1.8, 3.2) (figure 7).

Opportunistic infection

The association between Opportunistic infection and the incidence of mortality was reported in four articles. The current meta-analysis showed that the likelihood of death among HIV/AIDS patients with opportunistic infection at the baseline was 3.43 (95%CI: 1.08, 10.8) (figure 8).

Anemia

The pooled hazard ratio of children in antiretroviral treated HIV/AIDS patients with low hemoglobin levels at initiation of HAART was 2.76 (95% CI: 1.9–3.9). The pooled hazard ratio of children diagnosed with anemia had 2.76 times the risk of death compared to its counterpart (Figure 9).

Nutritional status

Having Malnutrition were factors significantly associated with mortality in antiretroviral treated HIV/AIDS -Positive children mortality. Those malnourished children at the baseline were 1.9 (95%CI: 1.3, 2.6) times more likely to die (figure 10).

Cotrimoxazole Preventive Therapy (CPT)

Based on the current meta-analysis, those receiving iron therapy were 66% less likely to die as compared to those who had not taken CPT (AHR: 0.34, 95% CI 0.05, 0.63). (figure 11).

Discussion

Assessing the effectiveness of ART in delaying disease advancement and reducing mortality in children deserves an urgent and wide-scale, evidence-based assessment(32). The cumulative incidence of death at different periods was not consistently reported by all the studies in Ethiopia. Therefore, the current systematic review and meta-analyses were aimed to synthesize the incidence of mortality and its predictors in antiretroviral treated HIV/AIDS -positive children. Based on the results of this review, the pooled incidence of mortality was 6.02 (95% CI: 3.7, 8.2) per 100 person-years of observation. There are very few

similar reviews comparable with our findings of pooled mortality estimates (33). Nevertheless, the current finding is higher than a study done in Malawi, Lesotho, and Swaziland(34) and Kinshasa, Democratic Republic of Congo(35).

This discrepancy might be due to the difference in the study period as there could be changes in the treatment and care modality of children on ART through time and a variation in ART enrollment time where the previous finding addressed children who started ART in earlier years with different treatment eligibility standard in which the WHO has made significant changes in ART initiation for pediatric irrespective of clinical or immunologic status(36, 37).

Additionally, it could be due to delayed ART initiation which increases the risk of advancing clinical staging, immune reconstitution inflammatory Syndrome, severe malnutrition, opportunistic infection, and drug toxicity and This difference could be due to a variation in ART enrollment periods where the previous studies addressed children who started ART in earlier years with different treatment eligibility criteria in which the WHO has made significant changes in the recommended pediatric age for ART initiation, regardless of clinical or immunologic status(36, 37).

Several multifaceted factors contribute to the uneven effect of pediatric HIV/AIDS in developing nations like stigmatization, cultural and social challenges to testing and treatment, inadequate health care set-up to support the patient, scarcity of trained health manpower in the field, scarcity of medical equipment and small qualified laboratory services(38). In Ethiopia, the cumulative pooled proportion of deaths was 9.2 % (95%CI: 6.8, 11.53). This result is consistent with the mortality rate reported in systematic review and meta-analysis (39) and a study in resource-limited countries (35). In contrast, a lower proportion of death was reported in the following studies (34, 40, 41).

As can be noted from the findings of this systematic review and meta-analysis, the predominant risk factors of mortality were being on the WHO clinical stage III/IV, lower CD4 cell count, and occurrence of opportunistic infections, anemia, and nutritional status. However, CPT was found to be preventive predictors.

The current study revealed that having a progressive WHO staging (stage III and IV) found to have a great impact on the occurrence of HIV/AIDS related to death. Those with progressive WHO staging (stage III and IV) were five-point three times more likely to die. This finding is congruent with previous studies conducted in different countries (33, 34) and Sub-Saharan Africa (39, 40).

The result of different studies revealed that lower CD4 cell count were the predominant predictors of mortalities (33, 35, 40). As CD4 count gets decline, the immune system of HIV/AIDS positive children would be very weak and leads to an increased vulnerability of OI, the most important case of child morbidities and mortalities(42). As evidenced by this study, baseline CD4 Cells count below the threshold for severe immunodeficiency was also another contributing factor for the incidence of mortality. This result was also supported by several studies (33, 35, 40). This

The presence of the opportunistic infection has also found to be a higher risk of death. Similar findings were reported in other studies conducted in Asia (43). As the patient started HAART in a more advanced stage and lower CD4 count, the risk of developing immune reconstitution syndrome and OI would be higher, which leads to an increase in the rate of viral replication(44).

The pooled hazard ratio with lower hemoglobin level (below 10gm/dl) at the initiation of ART was also higher as compared to its counterpart which was supported by studies from a study done in Sub-Saharan Africa (39). Hematological complications such as Zidovudine(ZDV) associated anemia are among the commonly reported adverse drug reactions of Antiretroviral Therapy(ART).

In our study, the incidence of death was significantly lower in children who were well-nourished than in those who were undernourished at baseline This finding is in line with other studies conducted in resource-deprived settings(35) and a study done in Kenya (33). The current meta-analysis revealed that patients who have taken CPT were 66% times less likely to die as compared to those who had not taken which in lines with the WHO guidelines which promote CPT implemented as an

integral component of a package of HIV-related services which prevent most of the opportunistic infections including tuberculosis which may reduce the rate of death(45, 46). **Strengths and limitations of the study:** As far as we know this is the first meta-analysis that has been done in Ethiopia. All of the included studies were with high methodological quality based on NOS assessment and similar study design. Despite this, our study had the following limitations. Like other meta-analyses, this study has several limitations that must be careful before interpreting results. the studies used for this analysis are not addressed all region of Ethiopia due to limited studies. Therefore, this could have a significant effect on inferring the finding.

Conclusion

This study noted that there was a high rate of mortality. Advanced WHO clinical staging (III/IV), lower CD4 cell count, presence of opportunistic infections, anemia, and undernutrition were factors associated with mortality in antiretroviral treated HIV/AIDS -Positive. In contrast, CPT was found to have a protective effect. Therefore, the health care provider and government need to emphasis on tedious screening of antiretroviral treated HIV/AIDS -positive children with low hemoglobin levels, advanced WHO clinical staging (III/IV), lower CD4 cell count, presence of opportunistic infections. Furthermore, CPT should be initiated as early as possible to all children regardless of clinical or immunologic status to reduce the incidence of childhood morbidity and mortality. Additionally, HIV infected children need frequent monitoring of growth and development, to detect growth faltering and developmental abnormalities early enough ad nutritional diversification shall be enhanced.

Declarations

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Authors' contributions

YA: Conceived and designed the study, reviewed literatures, extracted and analyzed data, interpreted results and drafted the manuscript. WS, TY, GD, AE, KG, BB ,HK, GY and AG involved in study selection, data collection, extraction, quality assessment and reviewing the manuscript. All the authors participate in supervision, analysis and interpretation, reviewed the manuscript thoroughly for its scientific content. All authors have read and approved the manuscript.

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Availability of data and materials

All data pertaining to this study are contained and presented in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow chart showing how the research articles were searched

Figure 2

Funnel plot of the included studies

Figure 3

Incidence of mortality among children on Antiretroviral treatment

Figure 4

Trim ad fills the analysis results of the included studies.

Figure 5

Sensitivity analysis of the included studies.

Line and Paragraph Spacing

Figure 6

The association between WHO clinical staging and the incidence of mortality

Figure 7

The association between baseline CD4 Cells count and incidence of mortality

Figure 8

The association between opportunistic infection and the incidence of mortality

Author/year

%

AHR (95% CI)

Weight

Dubeet al. (2017)

3.30 (1.87, 5.82)

38.64

Sidamo et al. (2014)

2.49 (1.35, 4.60)

33.01

Sidamo et al. (2014)

2.44 (1.26, 4.73)

28.35

Arage et al. (2018)

(Excluded)

0.00

Overall (I-squared = 0.0%, $p = 0.732$)

2.76 (1.94, 3.93)

100.00

NOTE: Weights are from random effects analysis

1

5

Figure 9

The association anemia and incidence of mortality

Figure 10

The association nutritional status and incidence of mortality

Figure 11

The association CPT and incidence of mortality