

# Burden of virologic failure, and its determinants among HIV positive children in East Africa: a systematic review and meta-analysis

Bogale Chekole Temere<sup>1\*</sup>, Agerie Aynalem Mewahegn<sup>1</sup>, Bitew Tefera Zewudie<sup>1</sup>, Fisha Alebel GebreEyesus<sup>1</sup>, Haymanot Abebe<sup>1</sup>, Ahmed Nuru<sup>1</sup>, Tamene Fetene<sup>1</sup>, Shegaw Tesfa<sup>1</sup>, Tadesse Tsehay Tarekegn<sup>1</sup>, Amare Kassaw<sup>2</sup>, Wubet Alebachew<sup>3</sup>, Belete Gelaw Walle<sup>4</sup>, Shegaw Geze Tenaw<sup>5</sup>, Yibeltal Mesfin<sup>5</sup>, Muche Argaw<sup>5</sup>, Daniel Tsega<sup>5</sup>

1. Department of Nursing, College of Medicine and Health Science, Wolkite University Southwest Ethiopia.
2. Department of Pediatric Nursing, College of Medicine and Health Science, Debre Tabor University, Northwest Ethiopia.
3. Department of Maternal & neonatal nursing, College of Medicine and Health Science, Debre Tabor University, NorthWest Ethiopia.
4. Department of Pediatric Nursing, College of Medicine and Health Science, Wolaita Sodo University, SouthWest Ethiopia.
5. Department of Midwifery, College of Medicine and Health Science, Wolkite University Southwest Ethiopia.

## Email address:

A. A- aynalemagerie21@gmail.com; S.G- shegaw.geze@gmail.com; B.T- bitewtefera1@gmail.com; A.K- amarekassaw2009@gmail.com; F. A- fishalebel@gmail.com; D.T- daniel2006tsega21@gmail.com; T.T- tadesse200912@gmail.com; T.F- tamenefet732@gmail.com; B.G beletegz12@gmail.com; Y.M- hazardkuku@gmail.com; M.A- mucheargaw@gmail.com; H.A- abebegeletie943@gmail.com; S.T- shegawtesfa201012@gmail.com; W.A- wubetalebachew@gmail.com; A.N- ahmednuuruu@gmail.com

## Abstract

**Background:** There are many studies regarding the prevalence of Virologic failure and its associated factors in East Africa, but they are inconclusive. In this study, the prevalence of Virologic failure and its associated factors in east Africa were determined.

**Methods:** Published articles that were conducted in English language were prepared based on preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. Web of Science, PubMed, and Google Scholar were explored to find out the articles. STATA Version 14 software was used for computing the pooled estimates of both the prevalence of virologic failure and associated factors. The pooled estimates were computed using both random and fixed effect models. Results were presented by using the random and fixed effect models. The pooled estimates were presented with 95% CI. Publication bias was assessed by looking the symmetry in the funnel plot.

**Result:** The pooled prevalence of virologic failure was, 25.90 (19.49, 32.32,  $p \leq 0.001$ ) in the random effect model. Four factors, poor adherence (2.91 (Pooled odds ratio (POR): 2.91, 95%CI: 1.93, 4.40), being male (1.17 (POR: 1.17, 95%CI: 1.08, 1.27)), wasting as an under nutrition (3.1 (POR: 3.1, 95%CI: 1.63, 5.95), and Nevirapine (NVP) based regimen (2.76 (POR: 2.76 (1.65, 95%CI: 4.62)) were found to be independent predictors of virologic failure.

**Conclusion:** The prevalence of virologic failure in East Africa is remarkably high. Four factors were found to be the determining factors. Different strategies must be designed to address (poor adherence, being male, wasting as an under nutrition, and NVP based regimen).

**Keywords:** HIV; virologic failure; adherence; viral load suppression.

**DOI:** <https://dx.doi.org/10.4314/abs.v24i3.2>

**Cite as:** Temere BC, Mewahegn AA, Zewudie BT, GebreEyesus FA, Abebe H, Nuru A, et al. Burden of virologic failure, and its determinants among HIV positive children in East Africa: a systematic review and meta-analysis. *African Health Sciences*. 2024;24(3). 1-9. <https://dx.doi.org/10.4314/abs.v24i3.2>

### Corresponding author:

Bogale Chekole Temere,  
Department of Nursing,  
College of Medicine and Health Science,  
Wolkite University Southwest Ethiopia  
Email: bogalechekole12@gmail.com

## Background

Virologic failure is considered when the viral load above or equal to 1000 copies/ml under ART based on two consecutive VL results 3 months apart, with adherence support following the first viral load test after at least 6 months of ART<sup>1</sup>.

Globally, a total of 1.8 million children (up to age 18 years) living with HIV and an estimated 110,000 AIDS-related deaths were reported<sup>2</sup>.

Sub-Saharan Africa and its sub region shares the higher global burden of HIV- infection<sup>3</sup>. There were evidences of Virologic failure from different countries across the globe. There were persistent disparities in the level of Virologic suppression, across countries' in Europe<sup>4</sup>. The prevalence of Virologic failure in Asian HIV positive children was 17.9%<sup>5</sup>.

Clinical, socioeconomic and factors that may be associated with Virologic failure vary between and within racial and ethnic groups<sup>6</sup>.

It is known that the goal of antiretroviral therapy is to suppress viral replication and reduce HIV related mortality among positive children. The World Health Organization (WHO) recommends routine viral load monitoring for all patients on ART. Since, Virologic failure believed to be early and accurate indicator for treatment failure during monitoring people on ART<sup>7</sup>.

However, there are studies conducted in Ethiopia and other East African countries, the findings were inconsistent and non-conclusive. So, the aims of this review were to estimate the pooled prevalence of Virologic failure and associated factors among HIV positive children in East Africa.

## **Methods**

### **Eligibility Criteria and Information Sources**

In this systematic review and meta-analysis, studies conducted in East Africa with an objective of assessing the prevalence of Virologic failure among HIV positive children were included. The studies were assessed using study area, title, abstract, and full texts prior to inclusion in this study. This study is prepared based on preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement<sup>8</sup>. In the current study, published articles that were conducted in English language were explored and included. The EndNote X5 reference manager was used to manage retrieved articles.

### **Search Strategy and Selection of Studies**

Electronic databases and reference lists of articles were explored by two investigators. Web of Science, PubMed, and Google Scholar were explored to find out the articles. Searching was conducted using key terms: children and adolescents as a population, factors, risk factors, and determinants as an exposure, prevalence, virologic fail-

ure, and treatment failure as an outcome, cohort studies, cross-sectional, and observational surveys as a study design, and East Africa, and East African countries as a study location. The Boolean search operators such as "OR" and "AND" were used during the searching process.

### **Data Extraction Process**

The structured data extraction checklist was used to collect information by two authors. Name of the author(s), publication year, and region as a study country, sample sizes, and the prevalence of virologic failure in proportion were extracted for this study.

### **Quality Assessment of Studies**

The two writers independently evaluated the included studies' merits using the National Institutes of Health (NIH) quality Assessment method to ascertain the research' caliber. As a result, each question received a "yes," "no," "cannot determine," "not applicable," or "not reported" response<sup>9</sup>.

### **Statistical Methods and Analysis**

In the present meta-analysis, STATA Version 14 software was used for computing the pooled 7 estimates of both the prevalence of virologic failure and its associated factors. The pooled estimates were computed using both random and fixed effect models. Results were presented by using the random effect models. Subgroup analyses were performed using the country as a region. The pooled estimates of factors were also presented separately. The pooled estimates were presented with 95CI. Meta-analyses were presented using forest plot, summary tables, and texts.

### **Publication Bias and Heterogeneity**

Publication bias was assessed by looking at the asymmetry of the funnel plot. Heterogeneities among studies were explored using forest plots and I<sup>2</sup> test. The sources of possible significant heterogeneities were explored through subgroup analyses and sensitivity analysis.

## **Results**

### **Selection of Eligible Studies**

As an initial search, we found 36 studies, retrieved from electronic databases (PUBMED, HINARI & others). From these studies 17 were duplicated files and 6 studies were removed after screening their titles and abstracts.

The full texts of 13 studies were reviewed. Finally, 10 studies (10-19) were included in the final analysis of this systematic review and meta-analysis (Fig 1).

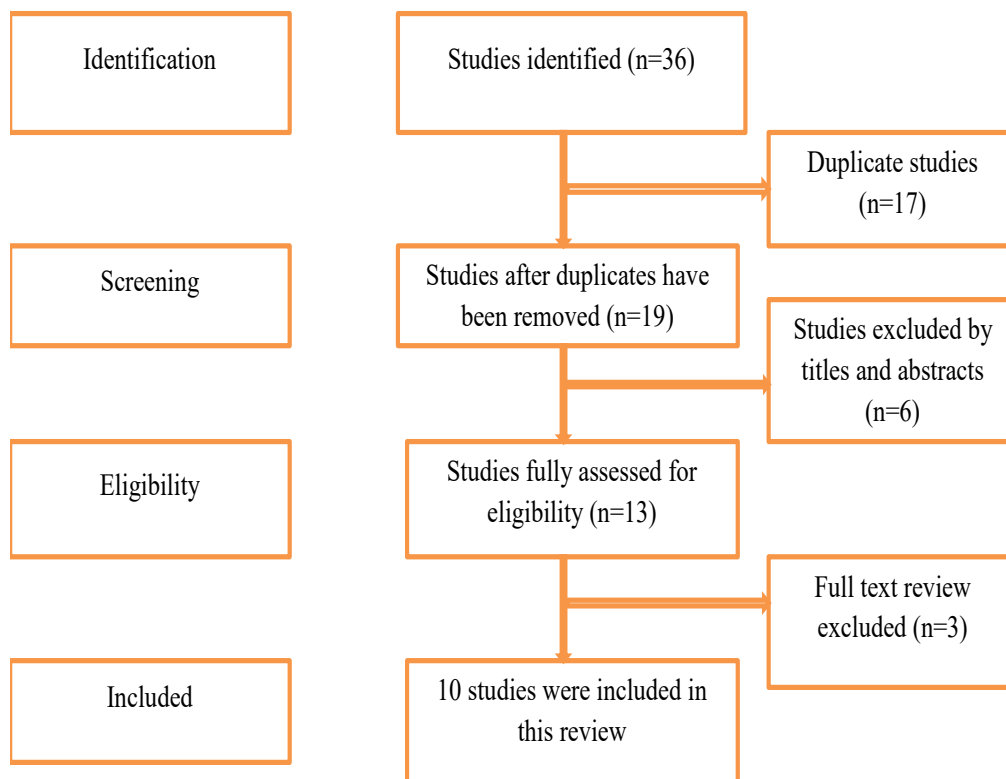


Figure 1: PRISMA flow chart showing the literature search processes for systematic and meta-analysis of virologic failure among children in East Africa(20).

### Characteristics of the Studies

From the studies included in this study 7 of them were cross-sectional and 3 of them were cohort studies. Re-

garding the study region, three studies from Ethiopia(11, 13), three studies from Tanzania(12, 17, 19), two studies from Uganda(15, 18) and two studies from Kenya(10, 16) were included (Table 1).

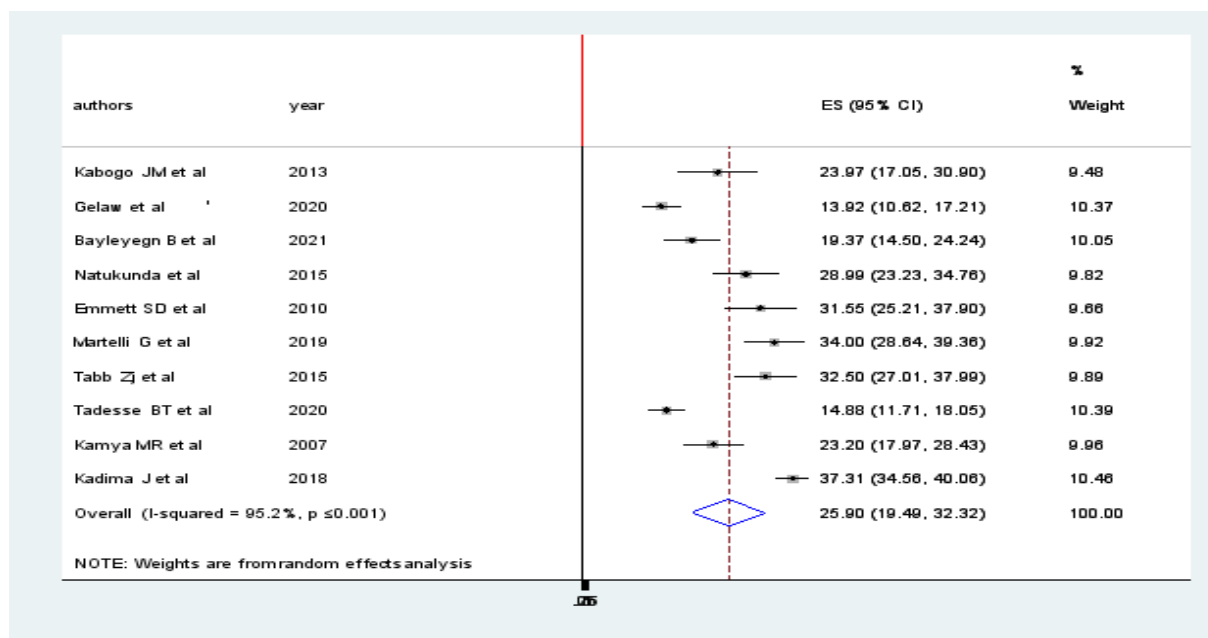
**Table 1:** Descriptive summary of seven studies in systemic and meta-analysis of virologic failure among children in East Africa.

Authors	Year	Region	Sample size	Cases	Study design	
Gelaw et al	2020	Ethiopia	424	59	cross-sectional	94.10%
Bayleyegn B et al	2021	Ethiopia	253	49	cross-sectional	100.00%
Tadesse BT et al	2020	Ethiopia	484	72	cross-sectional	100.00%
Kabogo JM et al	2013	Kenya	146	35	cohort	100%
Emmett SD et al	2010	Tanzania	206	65	cross-sectional	100.00%
Martelli G et al	2019	Tanzania	300	102	cross-sectional	100.00%
Tabb Zj et al	2015	Tanzania	280	91	cross-sectional	81%
Natukunda et al	2015	Uganda	238	69	cross-sectional	84.00%
Kamya MR et al	2007	Uganda	250	58	cohort	89%
Kadima J et al	2018	Kenya	1190	444	cohort	100.00%

### The Pooled prevalence of virologic failure

The prevalence of viral failure was lowest (13.92%) and highest (37.31%) in studies done in Ethiopia and Ken-

ya, respectively. In the random effect model, the pooled prevalence of Virologic failure was 25.90 (19.49, 32.32, p 0:001) (Fig 2).

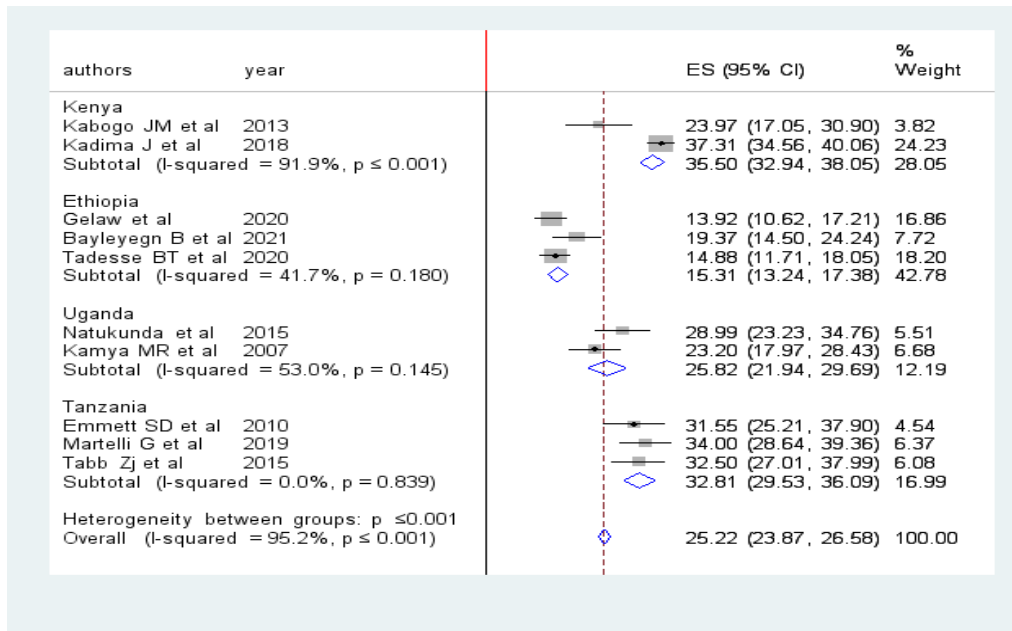


**Figure 2:** Forest plot in the pooled prevalence of virologic failure among HIV positive children in East Africa.

### Subgroup analysis of prevalence of virologic failure

Subgroup analysis by region was performed to compare the prevalence of virologic failure among children across countries in East Africa. Accordingly, the highest prev-

alence was observed in Kenya 35.50 (32.94, 38.05) followed by Tanzania 32.81 (29.53, 36.09) and the lowest prevalence 15.31 (13.24, 17.38) was observed in Ethiopia (fig 3).

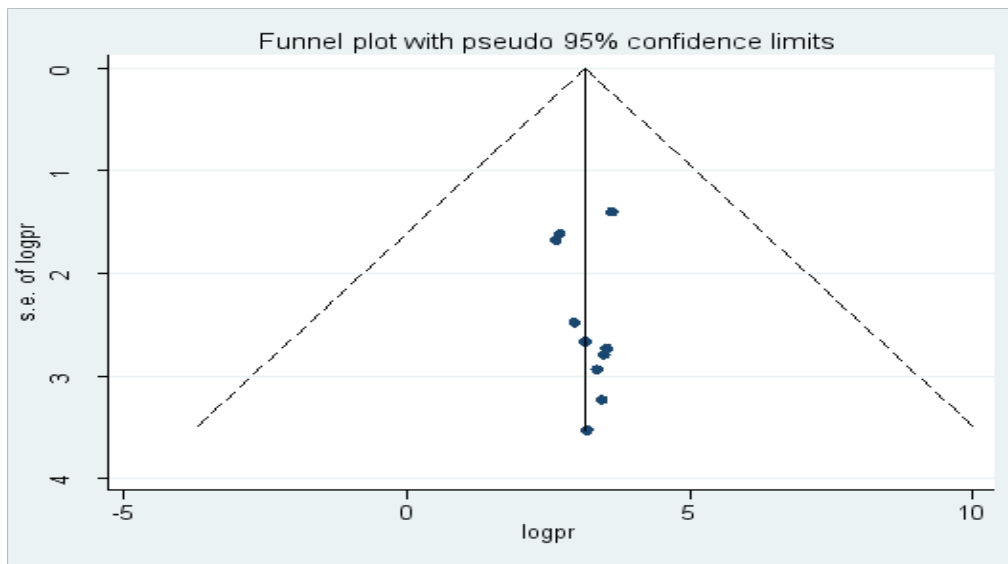


**Figure 3:** Forest plot showing the subgroup analysis of the pooled prevalence of virologic failure among HIV positive children in East Africa.

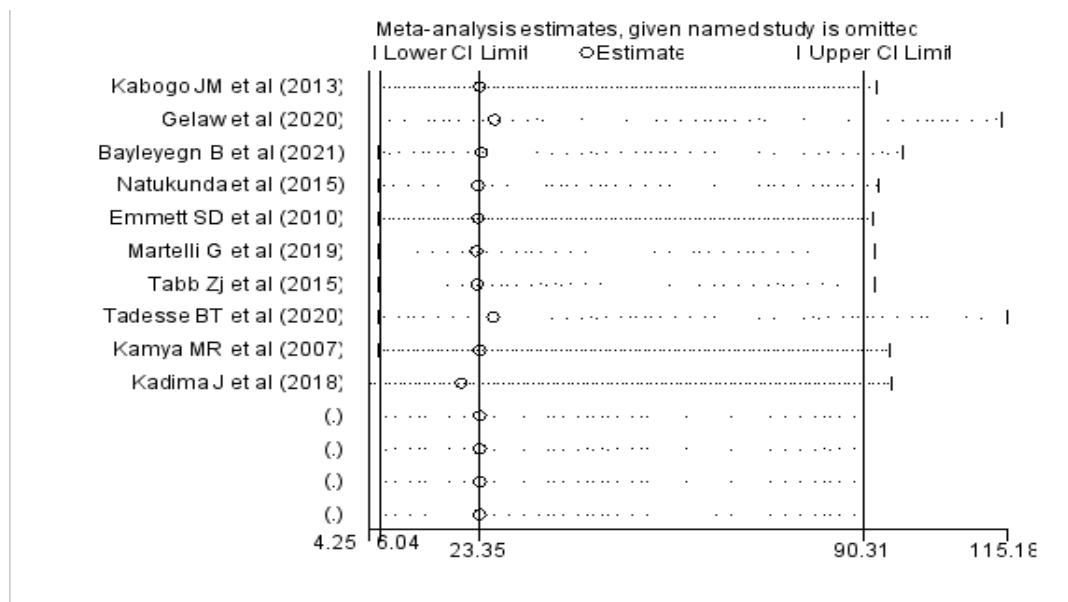
### Heterogeneity and publication bias

We assessed for the presence of publication bias among the studies included in the review by using a funnel plot.

There was a symmetrical distribution of the included studies through visual inspection, which indicates there was no potential publication bias (Fig 4).



**Figure 4:** Funnel plot showing publication bias among studies used to compute the prevalence of virologic failure among HIV positive children in East Africa. Sensitivity analysis was also done and it was found that no single study affected the pooled prevalence (Fig 5).



**Figure 5:** Sensitivity analysis of studies used to compute the prevalence of virologic failure among HIV positive children in East Africa.

### Factors associated with Virologic failure among children in East Africa

Seven studies<sup>11-14, 16, 18, 19</sup> were included in the analysis of the factors of virologic failure among children in East Africa. Four factors were included in this meta-analysis: poor adherence, being male, wasting as an under nutrition, and NVP based regimen. All of these factors were independent predictors of virologic failure. Male children were 1.17 (POR: 1.17, 95%CI: 1.08, 1.27) times more

likely to develop virologic failure as compared to females. The odds of developing virologic failure among children with poor ART adherence were 2.91 (POR: 2.91,95%CI: 1.93, 4.40) times higher as compared to those with good adherence. The odds of developing virologic failure among children who were on NVP based regimen 2.76 (POR: 2.76 (1.65,95%CI: 4.62) times higher. Severely wasted children were 3.1 (POR: 3.1, 95%CI: 1.63, 5.95) times more likely to develop virologic failure.

**Table 2:** Factors associated with virologic failure among HIV positive children in East Africa.

Factors	Included studies	OR (95%CI)	POR (95%CI)	Heterogeneity
Poor adherence	Tadesse BT et al	3.9(1.1,13.4)		
	Martelli G et al	3.22(1.87,5.56)		
	Gelaw et al	2.19(1.05,4.57)	2.91(1.93, 4.40)*	I <sup>2</sup> =0.92, p =
NVP based regimen	Kamya MR et al	2.46(1.23, 4.9)		
	Martelli G et al	3.19(1.47,6.89)	2.76(1.65, 4.62)*	I <sup>2</sup> =0.24, p =
Sex (Male)	Kadima J et al	2.2(1.3,3.8)		
	Jorojick et al	1.14(1.04,1.23)		
	Kamya MR et al	2.44(1.2,4.93)	1.17(1.08, 1.27)*	I <sup>2</sup> =9.85, p =
Severe wasting	Bayleyegn B et al	3.02(1.19,7.67)		
	Kadima J et al	3.2(1.3,7.9)	3.1(1.63, 5.95)*	I <sup>2</sup> =0.01, p =

CI: confidence interval, OR: odds ratio, NVP: Nevirapine, POR: pooled odds ratio



## Discussion

The pooled prevalence of virologic failure was computed using both fixed and random effect models. But, the final estimates were reported using the random effect model, since there was remarkable heterogeneity among studies (I<sup>2</sup>, 95.2%,  $p \leq 0.001$ ). The pooled prevalence of virologic failure in East Africa was 25.9%. Due to high heterogeneity among the included studies, these pooled estimates were presented with a random effect model. In this study, sub-group analyses were performed to estimate the pooled prevalence of virologic failure for countries in East Africa. The pooled prevalence of virologic failure in Ethiopia, Tanzania, Uganda, and Kenya were 15.31%, 32.81%, 25.82%, & 35.5% respectively. Finally, sensitivity analysis was performed, there was observed heterogeneities between the included studies. The possible source of heterogeneity might be the presence of variation in the prevalence of virologic failure in East African countries. From this finding, the pooled prevalence of virologic failure is remarkably higher in Kenya. This could be due to the high burden of poor ART adherence in the country. Regarding the factors, Virologic failure in male children was significantly higher as compared to females. This finding is supported by previous studies<sup>21, 22</sup>. This might be due to physiological differences. Similarly, the odds of virologic failure in children with poor ART adherence are considerably higher than those with good adherence. This is supported by previous studies<sup>23</sup>. The possible explanation for this is due to poor adherence patients will develop drug resistance, which will in turn cause the development of virologic failure<sup>24</sup>. Severe wasting was also an independent factor of virologic failure. The possible rationale might be the effect of malnutrition on the bioavailability of ART drugs<sup>25</sup>. Besides this, NVP based regimen was found to have a significant association with virologic failure and it is supported by a previous studies<sup>26-28</sup>. The other possible rationales for those identified factors need to be explored by future researches.

However, this study has strength in finding all possible articles; the presence of scant studies in the two countries could mask some other factors of virologic failure in East Africa. It had a risk of bias, incomplete retrieval of identifying research and reporting bias. Since most of the studies included in this review were cross-sectional, it is impossible to establish cause and effect relationship. The other limitation in this systematic review was all countries

of East Africa did not include it, so it might lack representativeness of the eastern African countries. Since the number of studies included in our sub-group analysis was small, the precision of the estimate might be reduced.

## Conclusion and recommendations

The prevalence of Virologic failure in East Africa is remarkably high. Four factors (poor adherence, being male, wasting as an under nutrition, and NVP based regimen) were found to be the determining factors. Different strategies must be designed by the nations of east Africa to address these factors to decrease the burden of Virologic failure in East Africa. We recommend prospective longitudinal researches to be done in the East African countries to identify all possible factors.

## Abbreviations

CI: Confidence interval.

HIV: Human immunodeficiency virus.

OR: Odds ratio.

POR: Pooled odds ratio.

UNAIDS: United Nations Programme on HIV/AIDS.

## Ethics approval and consent to participate

Ethical approval was not applied in this study because this was a review article and did not involve any participants.

## Consent for publication

Non applicable.

## Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request and will be attached to the editorial office when requested at any time.

## Competing interests

The author(s) declared no potential conflicts of interest concerning the research, authorship, and Publication.

## Authors' contributions

B.C. searched articles, analysed & interpreted the data, and wrote the main manuscript, B.T. searched articles and reviewed the manuscript, F.A. searched articles & reviewed the manuscript, A.K. searched articles & reviewed the manuscript, B.G. searched articles & reviewed the

manuscript, S.G. searched articles and reviewed the whole manuscript, H.A. searched articles & reviewed the manuscript, D. T. searched articles & reviewed the manuscript, T.T. searched articles & reviewed the manuscripts'. T.F. searched articles & reviewed the manuscript, A.A. searched articles, checked quality using check list, reviewed the manuscript, and searched articles Y.M. reviewed the manuscript, M.A. Searched articles & reviewed the manuscript. W.A. Searched articles, checked quality using check list & reviewed the manuscript. A.N. Searched articles, checked quality using check list, & reviewed the manuscript.

### Funding

The author(s) declared no financial support for this research.

### Acknowledgments

We are thankful to the authors of the original studies included in this systematic review and to those who contributed to this work.

### References

1. EMOH. National comprehensive HIV prevention, care and treatment training for health care provider's participant manual. January, 2018.
2. Global H. AIDS statistics—2018 fact sheet. Geneva: UNAIDS. 2019.
3. Amuche NJ, Emmanuel EI, Innocent NE. HIV/AIDS in sub-Saharan Africa: current status, challenges and prospects. 2017.
4. Laut K, Shepherd L, Radoi R, Karpov I, Parczewski M, Mussini C, et al. Persistent disparities in antiretroviral treatment (ART) coverage and virological suppression across Europe, 2004 to 2015. *Eurosurveillance*. 2018;23(21):1700382.
5. Mu W, Bartlett AW, Bunupuradah T, Chokephaibulkit K, Kumarasamy N, Ly PS, et al. Early and late virologic failure following virologic suppression in HIV-infected Asian children and adolescents. *Journal of Acquired Immune Deficiency Syndromes*. (1999). 2019;80(3):308.
6. Bhagwat P, Kapadia SN, Ribaud HJ, Gulick RM, Currier JS, editors. Racial disparities in virologic failure and tolerability during firstline HIV antiretroviral therapy. Open forum infectious diseases; 2019: Oxford University Press US.
7. Organization WH. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in

HIV-infected adults, adolescents and children, March 2018: supplement to the 2016 consolidated guidelines of the use of antiretroviral drugs for treating and preventing HIV infection. 2018.

8. McInnes MD, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA*. 2018; 319(4):388-96.

9. Health NIo. Study quality assessment tools: Quality assessment tool for observational cohort and cross-sectional studies. 2020.

10. Kabogo JM. Prevalence and risk factors of virologic failure and HIV-1 drug resistance among children and adolescents in Nairobi, Kenya: JKUAT-COHES; 2019.

11. Tadesse BT, Foster BA, Latour E, Lim JY, Jerene D, Ruff A, et al. Predictors of Virologic Failure Among a Cohort of HIV-infected Children in Southern Ethiopia. *The Pediatric Infectious Disease Journal*. 2020; 40(1):60-5.

12. Jorojick D. Predictors of the first line treatment failure in HIV infected children who are on second line art treatment in Tanzania: Muhimbili University of Health and Allied Sciences; 2020.

13. Bayleyegn B, Kifle ZD, Geremew D. Virological failure and associated factors among children receiving anti-retroviral therapy, Northwest Ethiopia. *Plos One*. 2021; 16(9):e0257204.

14. Gelaw B, Mulatu G, Tesfa G, Marew C, Chekole B, Alebel A. Magnitude and associated factors of virological failure among children on ART in Bahir Dar Town public health facilities, Northwest Ethiopia: a facility based cross-sectional study. *Italian Journal of Pediatrics*. 2021; 47(1):1-9.

15. Natukunda J, Kirabira P, Ong KIC, Shibanuma A, Jimba M. Virologic failure in HIV-positive adolescents with perfect adherence in Uganda: a cross-sectional study. *Tropical Medicine and Health*. 2019; 47(1):1-10.

16. Kadima J, Patterson E, Mburu M, Blat C, Nyanduko M, Bukusi EA, et al. Adoption of routine virologic testing and predictors of virologic failure among HIV-infected children on antiretroviral treatment in western Kenya. *Plos One*. 2018; 13(11):e0200242.

17. Tabb ZJ, Mmbaga BT, Gandhi M, Louie A, Kuncze K, Okochi H, et al. Antiretroviral drug concentrations in hair are associated with virologic outcomes among young people living with HIV in Tanzania. *AIDS (London, England)*. 2018; 32(9):1115.



18. Kanya MR, Mayanja-Kizza H, Kambugu A, Ba-keera-Kitaka S, Semitala F, Mwebaze-Songa P, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2007; 46(2):187-93.
19. Martelli G, Antonucci R, Mukurasi A, Zepherine H, Nöstlinger C. Adherence to antiretroviral treatment among children and adolescents in Tanzania: comparison between pill count and viral load outcomes in a rural context of Mwanza region. *Plos One*. 2019; 14(3):e0214014.
20. Bitew ZW, Alemu A, Ayele EG, Jember DA, Haile MT, Worku T. Incidence Density Rate of Neonatal Mortality and Predictors in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. *International Journal of Pediatrics*. 2020; 2020.
21. Penot P, Héma A, Bado G, Kaboré F, Soré I, Sombié D, et al. The vulnerability of men to virologic failure during antiretroviral therapy in a public routine clinic in Burkina Faso. *Journal of the International AIDS Society*. 2014; 17(1):18646.
22. Boullé C, Kouanfack C, Laborde-Balen G, Boyer S, Aghokeng AF, Carrieri MP, et al. Gender differences in adherence and response to antiretroviral treatment in the Stratall trial in rural district hospitals in Cameroon. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2015; 69(3):355-64.
23. Intasan J, Bunupuradah T, Vonthanak S, Kosalaraksa P, Hansudewechakul R, Kanjanavanit S, et al. Comparison of adherence monitoring tools and correlation to virologic failure in a pediatric HIV clinical trial. *AIDS Patient Care and STDs*. 2014; 28(6):296-302.
24. Li JZ, Paredes R, Ribaud HJ, Svarovskaia ES, Kozal MJ, Hullsiek KH, et al. Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure. *Aids*. 2012; 26(2):185-92.
25. Bartelink IH, Savic RM, Dorsey G, Ruel T, Gingrich D, Scherpbier HJ, et al. The effect of malnutrition on the pharmacokinetics and virologic outcomes of lopinavir, efavirenz and nevirapine in food insecure HIV-infected children in Tororo, Uganda. *The Pediatric Infectious Disease Journal*. 2015; 34(3):e63.
26. Shearer K, Brennan AT, Maskew M, Long L, Berhanu R, Sanne I, et al. The relation between efavirenz versus nevirapine and virologic failure in Johannesburg, South Africa. *Journal of the International AIDS Society*. 2014; 17(1):19065.
27. Zhang T, Ding H, An M, Wang X, Tian W, Zhao B, et al. Factors associated with high-risk low-level viremia leading to virologic failure: 16-year retrospective study of a Chinese antiretroviral therapy cohort. *BMC Infectious Diseases*. 2020; 20(1):1-9.
28. Rasoolinejad M, Sarraf M, Najafi Z, SeyedAlinaghi S, Moradmamand Badie B, Salehi M, et al. Virologic Failure in Different Antiretroviral Regimens Among Pediatric Patients with HIV Referring to a Voluntary Counseling and Testing (VCT) Center in Tehran, Iran (2004-2017). *Archives of Pediatric Infectious Diseases*. 2019; 7(4).