Research Square

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Using Viral Load as the Treatment Failure among Children on Antiretroviral Therapy: A Systematic Review and Meta-analysis

Hunduma Dina Hambisa

hunde4mother@gmail.com

Wollega University

Alemu Merga Hailu

Wollega University

Diriba Etana Tola

Assosa University

Betel Bogale Workineh

Wollega University

Wubet Tazeb Wondie

Ambo University

Bruck Tesfaye Legesse

Wollega University

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Abstract

Introduction: Traditionally, antiretroviral treatment monitoring was measured by different laboratory indexes, which was not reliable. Currently, the treatment progress of children on antiretroviral therapy is commonly evaluated by monitoring the viral load.

Methods: The 2020 PRISMA guideline was used as the study selection tool. Databases like EBSCOhost, ScienceDirect, EMBASE, Web of Science, Scopus, and PubMed were searched. EndNote 8 was used for citation and to remove duplicated studies. The 95% confidence interval and relative risk of identified factors were retrieved. To conduct meta-analysis, the random effects model and R statistics version 4.4.3 software were used.

Result: The total of 5253 children on antiretroviral therapy were selected from 16 studies. The pooled virological failure was 19% [95% CI: 15, 23]. Subgroup analysis was performed at $I^2 = 93.1\%$ and $p = 0.0001$. Factors frequently associated with virological failure were poor ART adherence, poor nutritional status, advanced clinical stage at initiation, and regimen change, with the risk ratios [95% CI: 4.74 (1.59, 14.13)] and [95% CI 4.59 (2.08; 10.14]), respectively.

Conclusion: Associated factors with virological failure identified by this meta-analysis: poor adherence, undernutrition, advanced clinical stage at initiation, and intolerance to regimen change significantly affected antiretroviral treatments among infected pediatrics.

Introduction

Globally, AIDS-related mortality was reported to be 6300,000 in 2022, and children accounted for 94,000 of those deaths[1]. In particular, Sub-Saharan Africa has the highest rate of pediatric HIV infection worldwide[2]. Although there is a global goal to eradicate pediatric HIV by 2015, children living with HIV in the sub-Saharan Africa continue to face a plethora of complicated problems [3].

Virologic suppression is the hallmark of successful HIV treatment in both adults and children. However, due to early immunologic damage and high viral loads found in many children, attaining rapid virologic suppression in children is critical[4]. Pediatric ART failure is an under-recognized issue that receives inadequate attention in the field of pediatrics and within HIV treatment programs[5]. **UNAIDS (2023) –** highlighted that **only 57%** of children living with HIV in sub-Saharan Africa achieved viral suppression in 2022, implying high levels of treatment failure[6].

Antiretroviral drugs are prescribed for life and need to be closely watched to ensure that they keep suppressing viruses to the maximum extent possible[7]. Monitoring the viral load is crucial for the early detection of treatment failure, adherence counseling, and avoiding unnecessary transfer of children to second-line treatment or delaying such a transfer[8].

In Ethiopia despite the scale-up of ART services and improvements in early infant diagnosis and pediatric HIV care, challenges such as poor adherence, drug resistance, limited access to viral load monitoring, and coexisting malnutrition continue to be challenge[9]. The burden is particularly high in rural and resource-limited settings where health system constraints and caregiver-related factors further complicate treatment adherence and follow-up [10].

Understanding the country level magnitude and determinants of virological failure is crucial for optimizing ART regimens, enhancing programmatic interventions, and ultimately improving the survival and quality of life of HIV-infected children[11].

Systematic review is a preferred method of recording, assessing and summarizing the state of knowledge on a particular topic based on the available evidence to make decisions used in the development of new strategies[12]. This finding will be used as a baseline for policy makers to modify HIV treatment and monitoring strategies for pediatric age group.

Research objectives

- To determine the national-level pooled magnitude of virological failure.
- **To identify the top risk factors associated with virological failure.**
- **To detect heterogeneity between the studies.**

Methods

Study protocol

The PRISMA guidelines for systematic reviews and meta-analyses served as the protocol to conduct this study [13]. Each step was completed independently by two different researchers. The third researcher investigated whether the findings agreed and settled any disputes **(Fig 1)**. The PRISMA check list also provided. **Supplemental material 1**. The protocol was registered on PROSPERO https://www.crd.york.ac.uk/PROSPERO/view/CRD4202460889.

Sources and search strategy

The primary studies searched in PubMed/Medline, Scopus, Science Direct, EMBASE, Web of Science (ISI), and EBSCOhost databases searching engine using Medical Subject Heading (MeSH): (Pediatric HIV infection OR children on ART OR Child hood HIV OR Pediatrics on HAART OR retroviral infection OR infant HIV), (Virological failure OR Suppressed viral load, Unsuppressed OR Treatment failure OR Viral load, pediatrics infection OR retroviral infected pediatrics OR Children on ART), (Predictors of virological prevalence OR Incidence of Virological suppression OR determinants of virological failure OR magnitude of ART failure OR factors associated with virological failure).**Supplemental material 2.**

Inclusion criteria and exclusion criteria

The PICO evidence-based medicine framework served as our basis for inclusion criteria, and nonrandomized studies met the following PICOS criteria[14].

PICO (population, intervention, comparator and outcome) of the study

Population (P): Children (pediatric, infants, adolescents)

Intervention (I): Antiretroviral therapy (ART)

Comparison (C): Not applicable (observational studies)

Outcome (O): treatment failure by virological load

Setting (S): Ethiopia

Operational definition: Virological failure is defined as a plasma viral load above 1000 copies/mL based on two consecutive viral load measurements following 3 months of adherence and taking ART for at least 6 months [15].

The following points were used as exclusion criteria.

(1) Studies included comorbidities with HIV infection

(2) Studies included more than 18-year-old participants

(3) Studies that reported immunological and mixed measurements

(4) Studies that reported non-operational out come

(5) Incomplete data, i.e., lack of variable of interest.

Quality assessment of included studies

Newcastle Ottawa Scale (NOS) checklist tool that uses 10 scales for nonrandomized studies was used [16, 17]. The tool included features for sampling, data collection, case definition, prevalence periods, and the validity and reliability of research instruments. Responses from the rating scale were classified as having a low risk of bias ("yes" answers to domain questions) or a high risk of bias ("no" answers to domain questions) for each article. Three categories were created based on the quality of the studies: poor (less than five points), fair (five to six points), and good (seven to eight points). If there was a disagreement, a group discussion was held. A score of five or more was needed to begin the meta-analysis process. **Supplemental material 3.**

Data extraction

The predesigned checklist, which comprised the following elements: patient characteristics, measures of virological failure, study design, publication year, setting, sample size, exposed group, non-exposed group to considered factors was used to extract data, and other inclusion criteria were studies published in the English language only.

Measurement of outcomes

The main outcome of this meta-analysis was to quantify national level pooled virological failure among children receiving antiretroviral therapy. This is the current standard monitoring of ART treatment and determines the

outcome. An additional goal was identifying consistent risk factors associated to virological failure.

Statistical analysis

The R version 4.4.3 statistical software was used to run entire analysis. The meta packages (*meta, metaAnalyser, metafor, metabias, and metadat*) was installed. The I^2 index and Cochran's Q test were used to assess the heterogeneity of the studies. The random effects model was applied in cases of moderate and high heterogeneity because there are three classifications in this regard: less than 25% is considered low heterogeneity, 25–75% is considered moderate heterogeneity, and more than 75% is considered high heterogeneity[18]. Subgroup analysis was performed based on the study area. Sensitivity analysis was also performed by omitting a study at a time. To detect publication bias, funnel plots, Begg's test, and Egger's test used.

Results

Description of included studies

Following the PRISMA screening procedure, 16 articles were ultimately selected for meta-analysis after comprehensive systematic review. The included studies are from Addis Ababa, the capital city [19-23], studies from the Oromia region [24-26], from the Amhara region [27-31], and at the national level[32-34]. (Table 1 and Fig. 1).

Table 1 Characteristics of the studies included in the meta-analysis

Authors	Publication year	Study design	Total Sample	Age of population	Study Area	Cases (%)	Response rate	JBI Quality Score
Alemayehu T,et al	2020	Cohort	74	5yrs -18yrs	Addis Ababa	13	100%	8
Bacha et al	2012	Cohort	259	1yrs-15yrs	Addis Ababa	108	95%	9
Bayleyegn B, et al	2021	cross-sectional	253	1yrs-18yr	Oromia	49	100%	8
Birrie E et	2022	Cohort	336	2yrs -15yrs	Amhara	47	100%	8
Bulti G,et al	2021	Case-control	316	2yrs -15yrs	National level	44	100%	6
Fozia T, et al	2020	Cohort	137	2yrs-18yr	Oromia	13	100%	8
Gelaw et al	2021	cross-sectional	399	2yrs -15yrs	Amhara	59	99%	9
Getaneh Y, et al	2019	Cohort	170	5yrs -15yrs	National level	51	97%	8
Getawa S, et al	2021	cross-sectional	201	1yrs -15yrs	Amhara	68	100%	9
Gidey G, et al	2020	Cross sectional	238	2yrs -15yrs	Addis Ababa	25	98%	7
Haile and Berha, et al	2019	Cohort	318	1yrs-18yrs	Amhara region	72	100%	8
Misasew M et al	2023	Cohort	250	2yrs-15yrs	Addis Ababa	42	100%	8
Shiferaw et al	2019	cross-sectional	1536	2yrs-15yrs	Amhara region	437	100%	7
Shumetie A, et al	2021	Case-control	159	1yrs -15yrs	National level	16	100%	8
Tilahun B, et al	2020	Cohort	193	1yrs-18yrs	Oromia	12	100%	7
Zenebe E, et al	2021	Cohort	414	1yrs -15yrs	Addis Ababa	110	100%	9

Graphical and statistical tests to analysis presence of publication bias

The funnel plot below showed minimal publication bias, further test like Egger's test and Begg's test also done**(Fig. 2)**.

Begg's and Egger's tests for publication

Kendall's tau (Begg's test) is a **non-parametric rank correlation** for Funnel Plot asymmetry, and Egger's test (regression analysis) was done by running the Freeman–Tukey Double Arcsine ("PFT") measure using the "*metafor*" package (Table 2).

Table 2 Begg's test and Egger's test of Publication bias

Number of studies=16		Method=REML
Test Statistic	**Test results**	**Implications**
Begg's test (Rank Correlation)	Kendall's tau = -0.2000 P = 0.3057	The Begg's test result depicts that there is no significant publication bias.
Egger's test (Egger's linear regression test)	z = -0.8921 P = 0.3724 (95% CI: b= 0.5493 (0.3304, 0.7682)	This test confirmed that there is no publication bias at the declared p-value

Even though the funnel plot shows minimal publication bias, Begg's more specific test and Egger's test confirmed the absence of publication bias, which may not require trim-fill analysis.

Leave-one-out sensitivity analysis

The pooled estimates remain largely consistent across all iterations, suggesting that the overall meta-analysis result is not overly sensitive to any single study. There is no extreme deviation when omitting any study, indicating no dominant or outlier study is distorting the result. The sensitivity analysis confirms that the meta-analysis findings are robust. Therefore, the conclusions drawn from the main analysis can be considered reliable and stable. **Supplemental material 4.**

Pooled Magnitude of Virological Failure

In this meta-analysis, by running a random effect model, the estimated overall pooled size of virological failure was 19% [(95% CI: 15, 23]), among children on antiretroviral therapy **(Fig 3)**.

Subgroup analysis by study area

Because of observed heterogeneity among the studies, a subgroup analysis was carried out based on the study settings. The subgroup analysis reported that the highest pooled magnitude of virological failure reported in the Amhara region 22% (95% CI: 16, 31) and the lowest was reported in the Oromia region 11% 95% CI: 5, 22) (**Fig. 4**).

Factors associated with virological failure

After screening and selecting pertinent studies, we focused on identifying frequently associated risk factors with virological failure among children on ART to conduct meta-analysis. After comprehensive review, we identified four risk factors significantly and consistently associated with virological failure from the selected articles: poor ART adherence status [95% CI: 4.74 (1.59, 14.13)], poor nutritional status [95% CI 4.59 (2.08; 10.14])], advanced clinical stage at initiation [95% CI: 3.24 (2.45, 4.29)], and regimen change [95% CI, 1.94 (1.15; 3.27])] (**Fig. 5**).

Discussion

For a variety of reasons, particularly children are vulnerable to virological failure; however, medical professionals tend to focus more on medication than on detecting the risk factors as opportunities and challenges.

The data from 16 studies selected hold 5253 samples of children on ART included in this meta-analysis to estimate the pooled magnitude of virological failure. Thus, the estimated magnitude of virological failure was found to be 19% [(95% CI: 15, 23]), which is similar to the studies conducted in Asian countries and Sub-Saharan 16.4% (13.9–19.4)[35]. However, this finding is lower than the studies conducted in South Africa (45%) [36], Tanzania (34%) [37], and Kenya but higher than the studies conducted in European countries [38], Uganda (13%) [39], and Cameron (4.9%) [40]. This difference might be because the populations of the abovementioned countries may differ in their knowledge and attitudes, pay varied attention to pediatric HIV treatment protocols and socioeconomic variations, or use community-based patient follow-up.

From subgroup analysis by study setting or region, the highest magnitude of virological failure was reported from the studies conducted in Amara region 22% (95% CI: 16, 31) from randomly selected health facilities, and the lowest magnitude was reported from the Oromia region 11% 95% CI: 5, 22). This variation might be due to sample size and poor adherence status of the patients and undernourishments.

Among the identified risk factors associated with virological failure, those who poorly adhered to take the pills were five times more likely to experience virological failure than those who had good adherence. This is in line with the study performed among Ugandan [41] and Central Tanzanian [37] children, which identified that poor adherence increases the risk of virological failure by 3 times. The explanations for this association are evidenced by low adherence to antiretroviral therapy, which enhances gene mutations resulting in drug resistance, consequently increasing viral load and leading to therapeutic failure in the pediatric population.

In these meta-analyses, undernourished children [5.71 (2.90, 11.26)] had four times the odds of virological failure among pediatrics when compared with well-nourished children. This report agrees with a systematic review conducted among low- and middle-income countries [42] and in southern Africa[43], showing that children who experience food poverty may skip doses when food is scarce, which exacerbates the viral load and prevents the suppression of viral copies. This finding suggests a relationship between food insecurity and low drug adherence.

Advanced clinical stage or third and fourth stages at treatment initiation increase the odds of virological failure by four times [95% CI, 4.35 (2.35, 8.04)], which is consistent with studies conducted in Mozambique[44] and Tanzania[45]. The reason could be that children in advanced WHO clinical stages are more likely to have advanced immune suppression and a higher rate of comorbidities; thus, the risk of ART failure could be higher in interventional studies in Ghana[46] and Namibia[47].

The possibility of virological failure was found to be doubled [95% CI, 2.49 (1.03, 6.03)] among children whose ART regimen changed. Evidence has outlined the children's family requests due to ART drug side effect intolerance and the preferences related to syrups associated with palatability and refrigeration[48, 49]. Some medications are delicious and simple to take. Some, like ritonavir, are not. The majority of liquid ART comes in heat-stable formulations; however, Ritonavir and Stavudine require refrigeration. In a similar situation, each drug dosage needs to be increased as child weight increases [50]. These frequent adjustments could confuse the caretaker, which would compromise adherence [51].

Conclusion

This meta-analysis revealed a significant magnitude of virological failure among pediatric patients receiving antiretroviral medication, although the treatment has long been available. Virological failure distribution was also found to be highly variable by subgroup analysis based on the study area. Antiretroviral therapies for pediatric patients living with HIV were found to be severely affected by the most common risk factors of virological failure: poor adherence, undernutrition, advanced clinical stage at initiation, and regimen changes.

Implications for Practice, Policy, and Future Research Implications

Clinically, healthcare providers should prioritize early identification of children at risk of virological failure by closely monitoring adherence, nutritional status, and treatment history, rather than focusing solely on pharmacologic interventions.

Policy-wise, there is a clear need for integrated pediatric HIV care with nutritional support, adherence counseling, and region-specific interventions, particularly in high-burden areas such as the Amhara region.

For future research, longitudinal and interventional studies are essential to further explore the causal relationships between virological failure and factors such as regimen changes, food insecurity, and advanced clinical stage at initiation. Personalized approaches that address socio-economic differences and health system limitations will be vital in reducing virological failure rates and improving pediatric HIV care outcomes.

Declarations

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Clinical trial registration number: Not applicable

Author contributions

"H.D., A.M., B.T., and B.B. contributed to proposal development. H.D. and B.T. participated in statistical analysis. H.D., A.M., B.B., and D.E. were involved in the design, selection of articles, and data extraction. H.D., B.B., W.T., and DE were involved in developing the initial drafts of the manuscript. All authors read and approved the final manuscript for submission."

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Availability of data

The datasets used and/or analyzed in the current work are accessible from the corresponding author upon reasonable request.

Ethical statement

Not applicable for the current study

Consent to participate

Not applicable

Consent for publication

Not applicable

Conflict of interest

The authors declare that they do not have any conflicts of interest.

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Figures

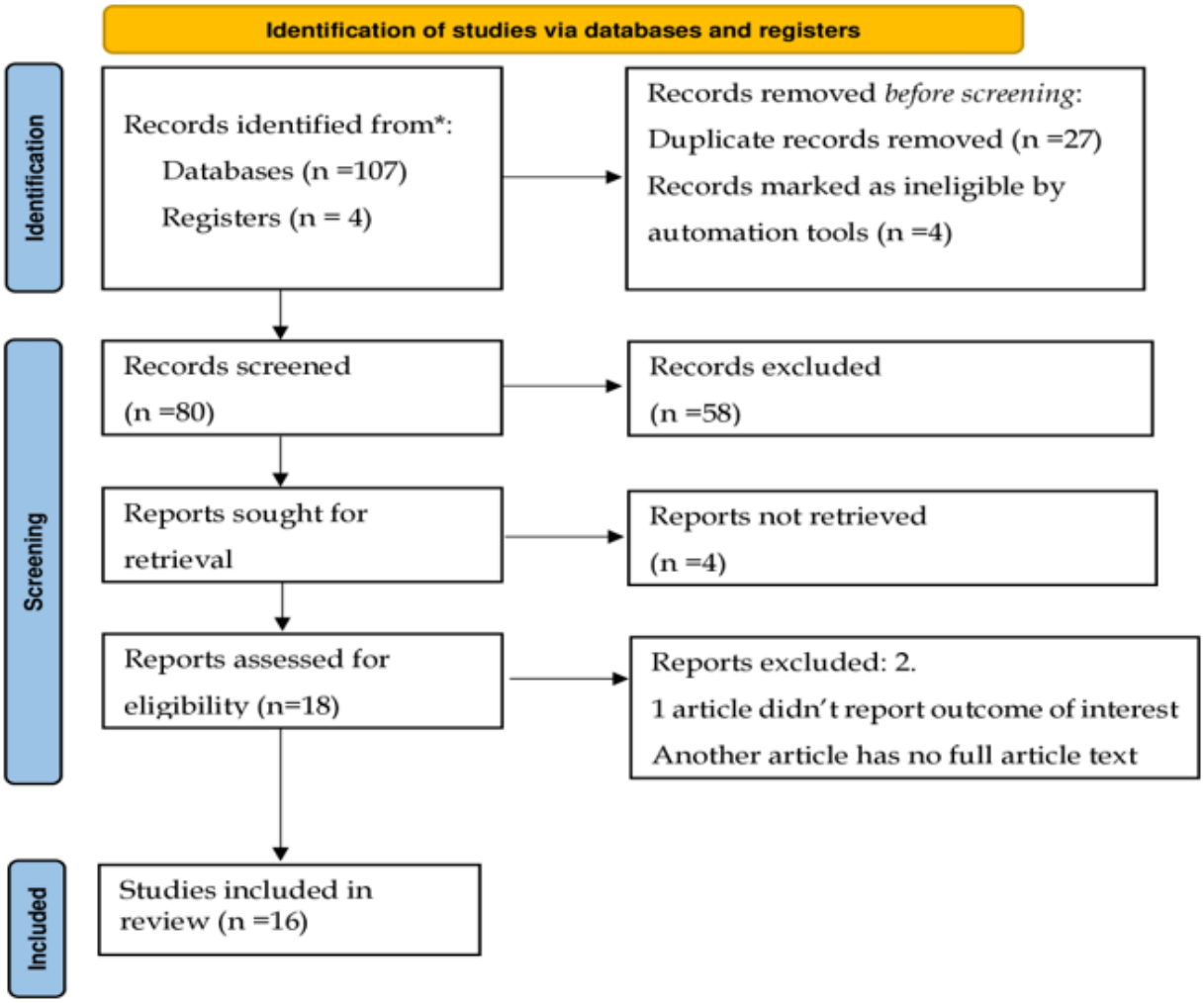


Figure 1

PRISMA follow diagram of the study screening steps for selection

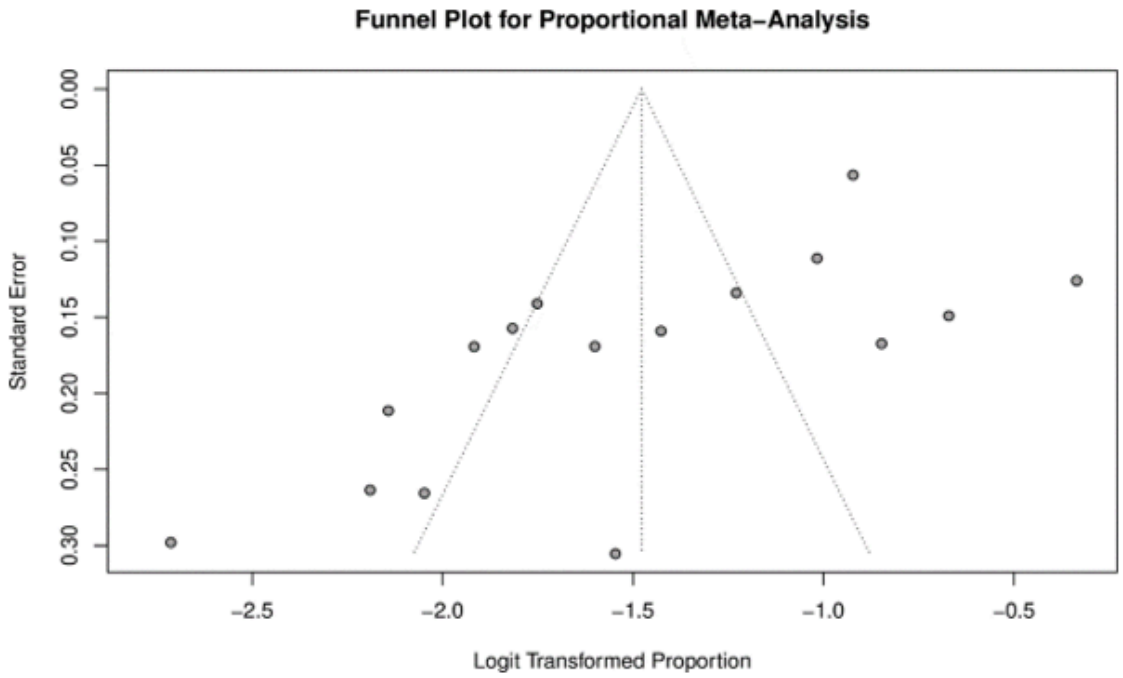


Figure 2

Funnel Plot to test visual publication bias of the studies

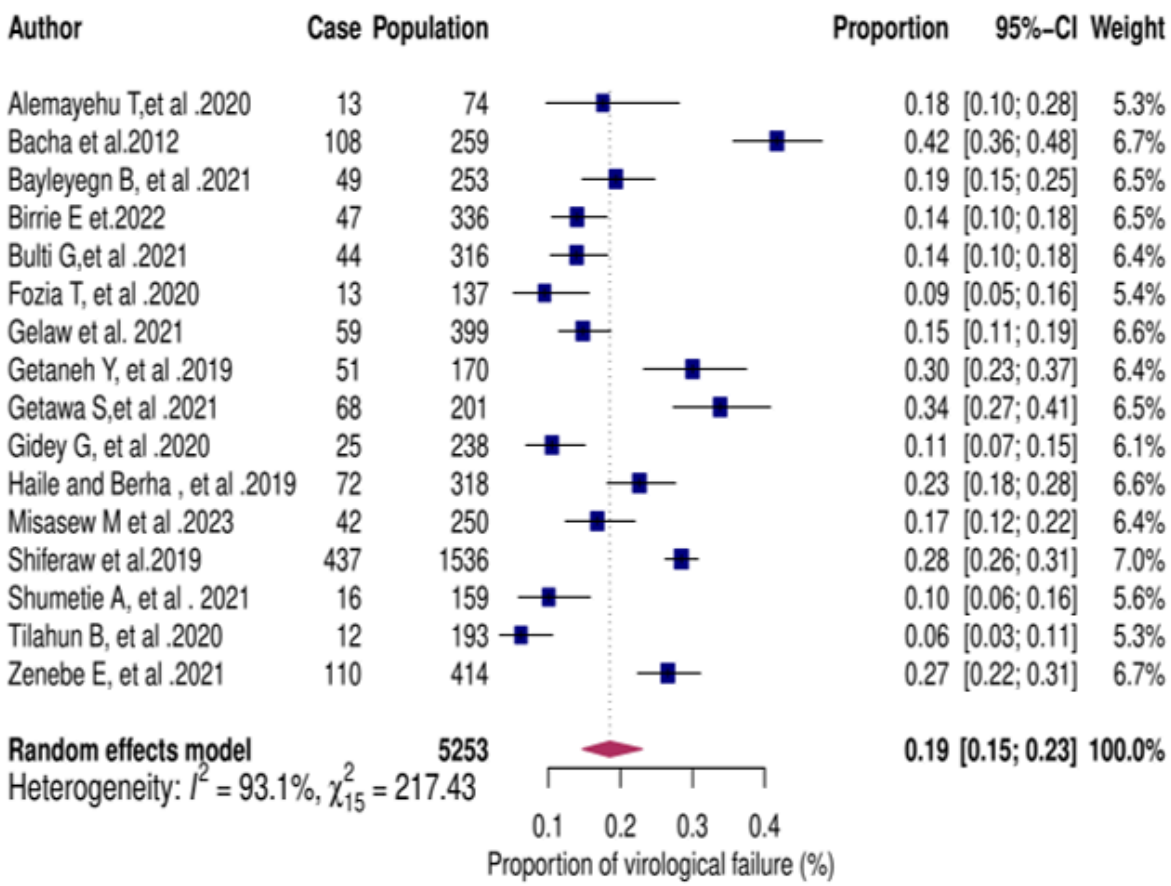


Figure 3

Pooled magnitude of Virological failure among Children on antiretroviral therapy

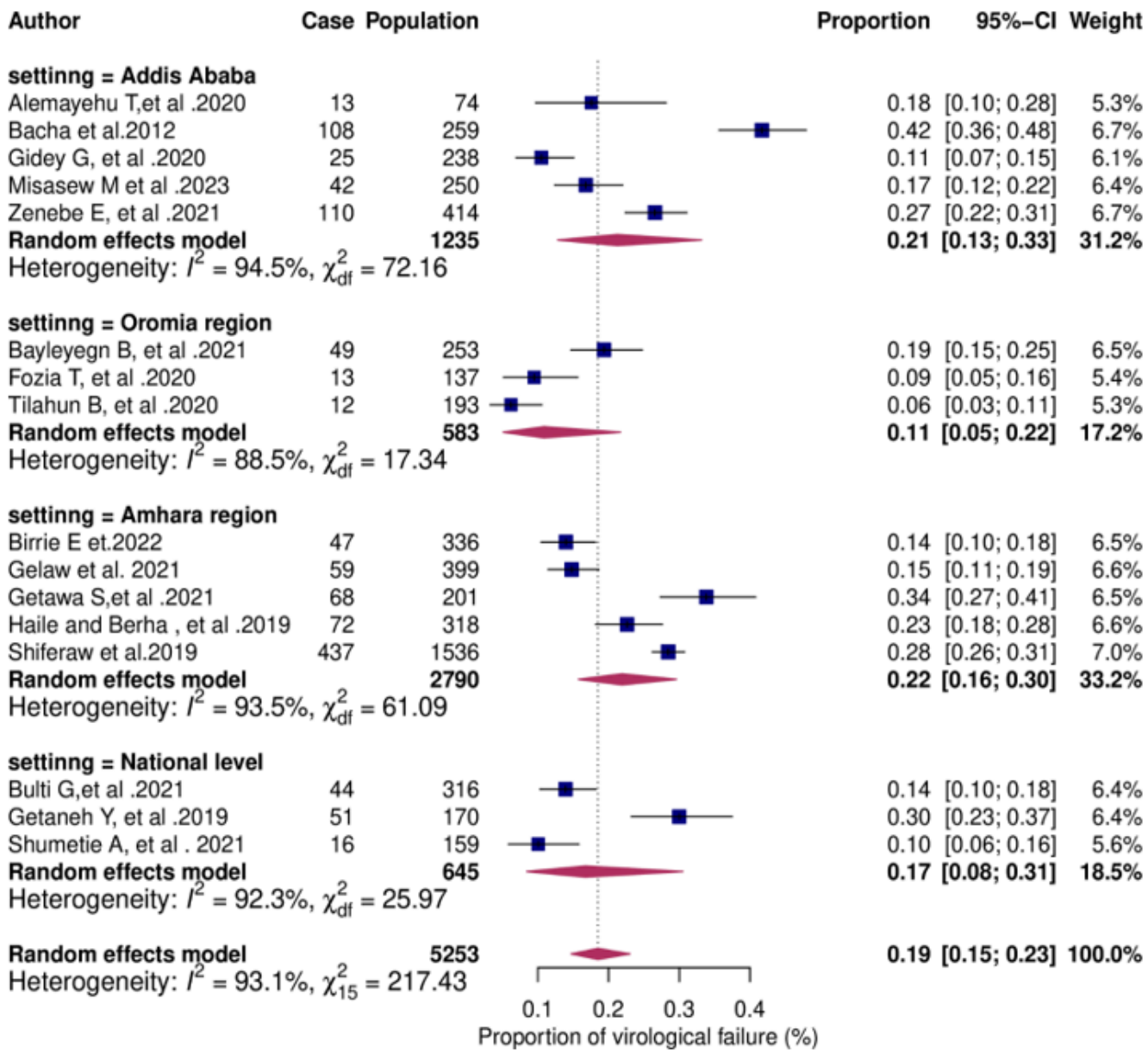


Figure 4

Subgroup description of Virological failure of Children on ART in Ethiopia

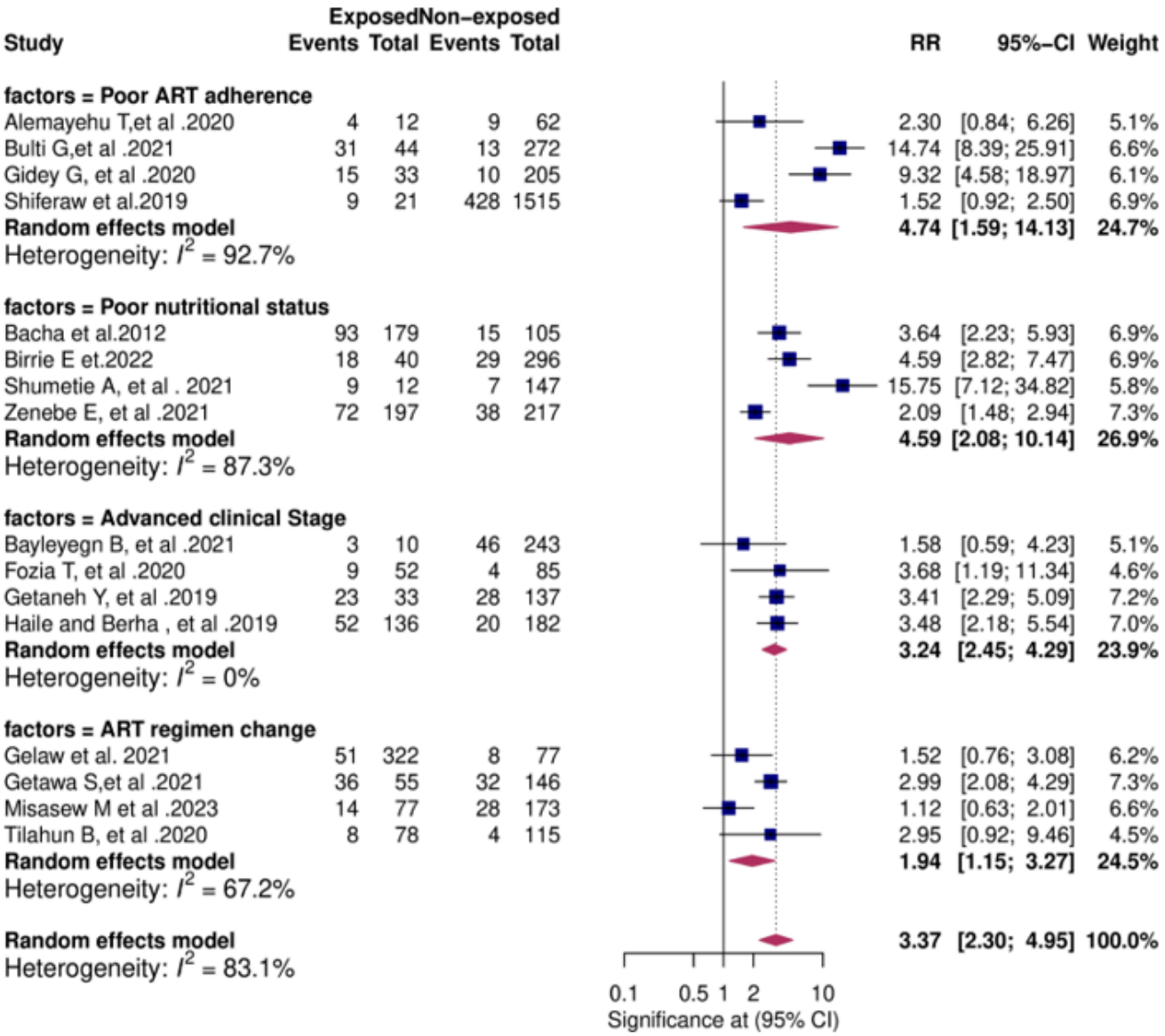


Figure 5

Common factors associated with Virological failure among Children on antiretroviral therapy.

Supplementary Files

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

- Supplementalmaterial1.docx
- Supplementalmaterial2.docx
- Supplementalmaterial3.docx
- Supplmentalmaterial4.tif