Magnitude and characteristics of unsuppressed HIV viral load in children and adolescents on antiretroviral therapy in sub-Saharan Africa: a systematic review and meta-analysis

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Summary

Background HIV/AIDS remains a major health issue in sub-Saharan Africa, especially among children and adolescents, with a substantial proportion of people with HIV having unsuppressed viral loads despite the availability of antiretroviral therapy (ART), complicating efforts to manage and control the epidemic. We aimed to estimate the prevalence of unsuppressed viral load and identify the factors contributing to this issue among children and adolescents living with HIV on ART in sub-Saharan Africa.

Methods In this systematic review and meta-analysis, we assessed data from Web of Science, Google Scholar, Scopus, PsycINFO, Embase, PubMed (MEDLINE), EBSCOhost Research Databases, and Wiley Online Library, as well as grey literature searches. We included studies published between Jan 1, 2010, and Nov 30, 2024 that focused on children and adolescents (aged <20 years) on ART in sub-Saharan Africa and reported on factors related to viral load suppression, defined by a viral load of less than 1000 copies per mL. Eligible studies included observational and interventional designs. Data appraisal and extraction were conducted by two independent reviewers from the author group, with summary data extracted from published reports. The primary outcome assessed was the prevalence of unsuppressed viral loads, with meta-analysis performed using STATA software to calculate prevalence and associated factors. The study is registered with PROSPERO (CRD42023451212).

Findings From an initial 13 121 identified articles, 52 studies involving 169 949 children and adolescents on ART met the inclusion criteria. Prevalence of unsuppressed viral load among children and adolescents in sub-Saharan Africa was 26·47% (95% CI 23·06–29·87); specifically, 26·01% (20·51–31·52) for studies in children (<15 years), 24·76% (17·36–32·16) for studies in adolescents (10–19 years), and 28·52% (23·33–33·72) for studies in a combined group of children and adolescents. Factors associated with unsuppressed viral load included younger age (<5 years), male sex, rural residence, orphan status, attendance at a level 1 or 2 health-care facility, HIV status not disclosed, poor ART adherence, advanced WHO clinical stage of HIV, low CD4 cell counts, history of opportunistic infections, nevirapine-based treatment regimen, drug substitution history, and not receiving co-trimoxazole prophylaxis. This meta-analysis showed a significant heterogeneity across the included studies, as evidenced by I^2=99·66% and p<0·0001.

Interpretation Unsuppressed viral load among children and adolescents is a key concern in sub-Saharan Africa, and is influenced by sociodemographic, clinical, immunological, and treatment-related factors. Addressing these issues through targeted interventions and improved ART adherence strategies is crucial for better health outcomes.

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Introduction

The scourge of HIV/AIDS has been one of the most daunting health challenges of the past few decades.[1] Antiretroviral therapy (ART) has transformed HIV from a fatal disease into a manageable condition, improving survival and quality of life for millions of people.[2] However, the fight continues, especially in sub-Saharan Africa, which bears two-thirds of the global HIV burden, underscoring the need for effective ART management.[3]

In 2023, 1·4 million (95% CI 1·1–1·7 million) of the 39·9 million people living with HIV globally were children younger than 15 years old.[3] Sub-Saharan Africa accounted for approximately 66% of all HIV cases and 86% of children younger than 15 years living with HIV worldwide.[3] Around 590 000 (430 000–920 000) children aged 0–14 years living with HIV did not have access to ART in 2023.[3] ART coverage among adolescents and adults aged 15 years and older was 77% (95% CI 62–90), but only 57% (41–75) among children younger than 15 years, with even lower viral load suppression rates: 48% (39–60) for children compared with 73% (66–81) for adolescents and adults. The persistent gaps in early diagnosis and access to effective treatment led to approximately 76 000 (53 000–110 000) child deaths in 2023, with 73% of these occurring in children younger than 10 years. Despite representing just 3% of people

Research in context

Evidence before this study

Before conducting this systematic review and meta-analysis, the authors reviewed existing literature on unsuppressed HIV viral loads among children and adolescents living with HIV in sub-Saharan Africa. Multiple databases were searched: Web of Science, Google Scholar, Scopus, PsycINFO, Embase, PubMed (MEDLINE), EBSCOhost, and Wiley Online Library. The search covered studies published from Jan 1, 2010 to Nov 30, 2024 (with no language restrictions). The search terms encompassed "children", "infant", "adolescent", "HIV-positive", "antiretroviral therapy", "viral load", "suppression", "unsuppressed", "virological failure", "risk factors", "determinants", and "predictors". The inclusion criteria specified studies that involved children and adolescents (aged <20 years) on antiretroviral therapy (ART), reported associations between risk factors and viral load suppression, and provided quantitative measures of suppression defined by a viral load of less than 1000 copies per mL. Exclusion criteria included studies published before 2010, review papers, case reports, papers with other definitions of viral load suppression, editorials, letters, and conference abstracts. Discrepancies were resolved through full-text evaluation, and attempts were made to contact authors for missing data.

Added value of this study

This study offers an updated and comprehensive analysis of the prevalence and factors associated with unsuppressed viral load among children and adolescents on ART in sub-Saharan Africa. Our review synthesises data from 52 studies involving 169 949 children and adolescents on ART, providing prevalence estimates for unsuppressed viral load: 26·01% for studies among children (age <15 years), 24·76% for studies among adolescents (age 10–19 years), 28·52% for studies in the combined age group, and 26·47% overall. Key factors associated with unsuppressed viral load include younger age (<5 years), male sex, rural residence, orphan status, attendance at a level 1 or 2 health-care facility, HIV status not disclosed, poor ART adherence, advanced WHO clinical stage, low CD4 cell counts, history of opportunistic infections, nevirapine-based regimen, drug substitution history, and no co-trimoxazole prophylaxis. This study contributes to the existing literature by not only filling gaps in previous research but also providing evidence for known factors associated with unsuppressed viral load, offering a more nuanced understanding of the challenges in reaching viral load suppression in this demographic.

Implications of all the available evidence

The combined evidence from this study and previous research emphasises the need for targeted interventions to improve ART adherence and optimise treatment regimens for children and adolescents in sub-Saharan Africa. The identification of these key factors associated with unsuppressed viral load suggests that interventions should address these factors, particularly in rural areas and among orphans. Future research should focus on evaluating the effectiveness of targeted interventions and exploring strategies to enhance adherence and treatment outcomes. Policy makers and health-care practitioners should leverage these findings to inform resource allocation, develop effective public health strategies, and work towards achieving the UNAIDS 95-95-95 targets.

living with HIV, children accounted for 12% of all AIDS-related deaths.[3]

The 95-95-95 UNAIDS strategic objective, aimed at ending the HIV/AIDS epidemic by 2030, seeks to ensure that 95% of people living with HIV know their status, 95% of those who know their status are on ART, and 95% of those on ART have suppressed viral loads.[4] The rapid expansion of ART availability in sub-Saharan Africa is a commendable achievement, yet its potential impact is undermined when viral load suppression is not reached or maintained.[5,6] Viral load suppression is the primary goal of ART, as it not only improves the health outcomes for the individual but also reduces the risk of HIV transmission to others. Despite these benefits, unsuppressed viral loads remain a substantial problem, particularly among children and adolescents on ART in sub-Saharan Africa.[7–10] This public health issue not only threatens the lives of the individuals affected but also poses a risk to the broader goal of controlling and eventually eradicating HIV/AIDS. Failure to achieve UNAID's 95-95-95 targets for children and adolescents in sub-Saharan Africa, means that new infections will continue to rise, and HIV-related mortality will persist for decades to come.[11]

Understanding the prevalence of unsuppressed viral load and its contributing factors is key for health-care policy, clinical management, and public health interventions. Our review aims to fill a crucial knowledge gap, especially for children and adolescents, who face unique challenges with lifelong ART, including stigma and discrimination.[12,13]

This review aimed to establish the meta-analysed prevalence of unsuppressed viral load among children and adolescents on ART in sub-Saharan Africa and examine the factors contributing to the magnitude of unsuppressed viral load at a regional level.

Methods

Search strategy and selection criteria

The study protocol was registered on the Prospero website (CRD42023451212) before data extraction, and the review complies with the PRISMA guidelines.[14]

Our literature search aimed to identify published studies with the following inclusion criteria: published in peer-reviewed journals or grey literature; population included children and adolescents (age <20 years) with HIV on ART; reported associations between risk factors and viral load suppression, using the WHO-defined

threshold of less than 1000 copies per mL,[15] with viral load measurements assessed at least 6 months after the initiation of ART to ensure that the evaluation of viral suppression reflects the effects of long-term treatment adherence and efficacy; and all studies from sub-Saharan Africa (2010–24). Exclusion criteria were adult-focused studies, pre-2010 publications, reviews, case reports, editorials, letters, conference abstracts, studies that used viral load thresholds other than the WHO-defined threshold of less than 1000 copies per mL, and studies that included both adults and children.

Two members of the author group (OM and YNK) identified studies on viral load suppression by searching multiple electronic databases: Web of Science, Google Scholar, Scopus, PsycINFO, Embase, PubMed (MEDLINE), EBSCOhost, and Wiley Online Library. Grey literature and manual searches were also conducted to find unindexed articles. We included publications on viral load suppression in children and adolescents with HIV, published between Jan 1, 2010 and April 30, 2024. The search strategy was tested and refined through initial database searches, then replicated and adjusted for other databases. In cases of missing data, two email attempts were made to contact corresponding authors before excluding the study.

The search used a list of relevant keywords and concepts and the relevant "AND" and "OR" Boolean operators to obtain full-text articles. The search terms consisted of "children", "infant", "adolescents", "HIV-positive", "antiretroviral therapy", "viral load", "suppression", "unsuppressed", "virological failure", "risk factors", "determinants", and "predictors". The search strategies used for the selected databases are provided in the appendix (pp 2–5).

We conducted this systematic review with a focus on countries in sub-Saharan Africa and included only quantitative observational studies (ie, cohort, case-control, and cross-sectional). We managed the identified studies using Covidence to track articles, remove duplicates, and manage references. We conducted data searches from Nov 23 to April 30, 2024, with an update on Nov 30, 2024 for new publications. Two reviewers (OM and YNK) independently screened and selected references and abstracts, resolving disagreements through discussion. We assessed the full texts of eligible studies following PRISMA Protocol 2020 guidelines[14] and evaluated their methodological quality with the Joanna Briggs Institute tool.[16] Discrepancies in study inclusion or risk of bias were addressed through discussion between the two reviewers or with the help of a third reviewer (SOW).

Each item was scored for risk of bias (1 for yes, 0 for no or unclear), and then converted to a percentage: ≤49% (high risk of bias), 50–69% (moderate), and ≥70% (low). Only studies with a score of 50% or higher were included. We used a Microsoft Excel matrix for data extraction, capturing details such as author, study year, location, objective, design, population, sample size, exposure factors, methods, outcomes, and findings. In longitudinal studies, only one viral load measurement taken at 6 months of ART was included in the analysis to ensure that each participant contributed only once to the meta-analysis, thereby preventing inflation of the sample size due to repeated measures. We recorded adjusted variables to control for confounding, documented unsuppressed viral load prevalence and risk factors, and verified data quality against published sources, contacting authors if needed.

Data analysis

Abstracted data were saved in Microsoft Excel and then exported to Stata 16 for meta-analysis. The event and non-event counts were extracted from the various studies to obtain the prevalence and odds ratios reported in this review. A random-effects model using the meta command in Stata was applied to estimate the prevalence and risk factors associated with unsuppressed viral load among children and adolescents. Significant associations with unsuppressed viral load were reported using an odds ratio (OR) with 95% confidence intervals (95% CIs). Forest plots were used to display the prevalence of unsuppressed viral load and its associated factors, along with 95% CIs. Subgroup analysis was conducted by study sub-region, study design, and study age group to examine variations in the prevalences. For the meta-analysis of studies on risk factors for unsuppressed viral load, we applied the random-effects model using the Hartung–Knapp–Sidik–Jonkman method to ensure a more accurate estimation of between-study heterogeneity.[17,18] Heterogeneity across studies was quantified using the I^2 statistic, for which values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively. A p value less than 0·05 (from Cochrane's Q test) was used to identify the presence of significant heterogeneity. For the assessment of publication bias, we applied a logit transformation of the prevalences to stabilise variance and improve normality, followed by a visual inspection using a funnel plot and statistical evaluation with Egger's regression test, for which a p value lower than 0·05 indicated significant publication bias. We aimed to include all studies in the analysis of bias.

See Online for appendix

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The search yielded 8101 articles from Web of Science, 1820 from Google Scholar, 1070 from Scopus, 930 from PsycINFO, 601 from Embase, 419 from PubMed, 151 from EBSCOhost, 29 from Wiley, and 20 from grey literature. After exclusions, 52 articles were included in the review (figure 1). During the data extraction process, we

observed variations between data extractors. Nonetheless, these variances were reconciled through discussions among the data extractors; following their consensus, the data were subsequently analysed.

Among the 52 studies included in this systematic review (table), the geographical distribution of the sub-regions of sub-Saharan Africa are as follows: eastern Africa represents the majority of the studies with 29 articles, followed by southern Africa with 14 articles, and western and central Africa are each represented in five studies. 11 studies were from Ethiopia,[19–29] nine from Tanzania,[10,30–36,55] six in Kenya,[37–42] five in Cameroon,[8,43–46] four in South Africa,[47–50] and three in each of Zimbabwe,[51–53] Malawi,[52,54,55] Uganda,[7,9,55] and Nigeria.[56–58] Two studies were in each of Mozambique[59,60] and Eswatini.[55,61] Additionally, one article was found for each of Botwana,[55] Ivory Coast,[62] Ghana,[63] Lesotho,[55] Namibia,[64] Rwanda,[65] and Zambia.[66]

In the 52 studies included, USVL was defined by a viral load of more than or equal to 1000 copies per mL (table). WHO recommends that a viral load of more than or equal to 1000 copies per mL is used to identify individuals needing closer monitoring or treatment interventions to prevent HIV transmission and manage ART effectiveness.[15]

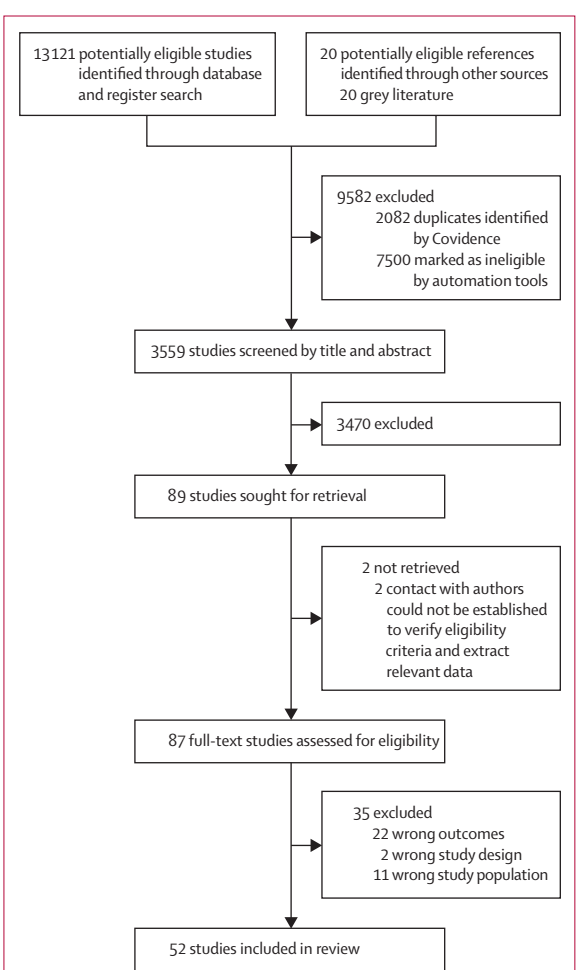

Figure 1: **Studies included to estimate prevalence of unsuppressed HIV viral load among children and adolescents living with HIV in sub-Saharan Africa**

38 of the studies used a cross-sectional design,[7,8,10,21,23–29,31–33,35,37–39,41–45,48–51,53,55–63,66] 14 used a cohort study design.[9,19,20,22,30,34,36,40,46,47,52,54,64,65] We included all studies published in internationally recognised journals between Dec 14, 2015 and Aug 28, 2024, based on searches up to Nov 30, 2024. The sample sizes of the included studies ranged from 140 to 34400.[26,35] All studies met the minimum quality standards according to the Joanna Briggs Institute quality appraisal criteria, with an average quality score of 91·7% across all studies (table).[16]

We included 52 articles with 169949 children and adolescents on ART to estimate prevalence of unsuppressed viral load in sub-Saharan Africa, grouping studies into three population-based subgroups (table): 20 studies including only children (age <15 years) with 45248 participants,[9,10,20,21,23,25–29,33,37,39,47,56,59,61–63,65] 15 studies including only adolescents (10–19 years) with 55038 participants,[7,8,24,35,36,41,43,45,48–51,58,64,66] and 17 studies including both children and adolescents (≤19 years) with 69663 participants.[19,22,30–32,34,38,40,42,44,46,52–55,57,60]

The prevalence of unsuppressed viral load among children and adolescents in sub-Saharan Africa was 26·47% (95% CI 23·06–29·87). However, this meta-analysis showed a significant heterogeneity across the included studies as evidenced by an I^2 of 99·66% (p<0·0001; figures 2–4), whereas a non-significant Egger's test (β1=–2·74, p=0·093) excludes the presence of publication bias (appendix p 6).

We performed subgroup analysis based on study subregion, study design, and study age group. The analysis by study sub-region of sub-Saharan Africa revealed differences in prevalence rates across the regions. Central Africa had a prevalence of 32·65% (95% CI 17·95–47·35), whereas eastern Africa showed a lower prevalence of 21·32% (17·66–24·97). In southern Africa, the prevalence was 29·33% (22·86–35·80), and western Africa had the highest prevalence at 41·06% (35·11–47·02). The test for group differences (Q=31·72, p<0·0001) revealed significant variations in prevalence rates between the sub-Saharan Africa sub-regions (figure 2).

The analysis by study design revealed variations in the prevalence rates across different types of studies. In cohort studies, the prevalence was 22·62% (95% CI 17·34–27·90), whereas cross-sectional studies showed higher prevalence of 27·86% (23·68–32·03). The test for group differences (Q=2·32, p=0·13) indicated that there were no statistically significant variations in prevalence rates across the study designs, suggesting a relatively consistent effect across these different study designs (figure 3).

	Sub-region of sub-Saharan Africa	Country in which the study was conducted	Study area (city, village, or region)	Study design	Study start	Study end	Population group	Age group	Risk factors for USVL	Total number of participants included	Number of patients with USVL	JBI score
Abera et al (2023)[22]	Eastern	Ethiopia	Oromia region	Cohort study	2015	2019	Children and adolescents	0–19 years	Poor treatment adherence, male sex, no disclosure, opportunistic infection, rural, low CD4 cell count, and advanced WHO clinical stage of HIV	492	85	91%
Afrane et al (2021)[63]	Western	Ghana	Accra	Cross-sectional study	October, 2017	July, 2018	Children	<15 years	Female sex, low CD4 cell count, past treatment of tuberculosis, and nevirapine-based regimen	250	96	100%
Ally et al (2023)[33]	Eastern	Tanzania	Arusha, Dar-es-Salaam, Dodoma, Geita, Iringa, Kagera, Katavi, Kigoma, Kilimanjaro, Mara, Mbeya, Mjini Magharibi, Morogoro, Mtwara, Mwanza, Njombe, Pwani, Rukwa, Ruvuma, Shinyanga, Simiyu, Singida, Songwe, Tabora, and Tanga	Cross-sectional study	October, 2018	September, 2020	Children	0–14 years	Poor treatment adherence, and no HIV status disclosure	1980	292	100%
Bacha et al (2022)[55]	Southern and Eastern	Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda	Gaborone, Mbabane, Maseru, Lilongwe, Kampala, Mbeya, and Mwanza	Cross-sectional study	January, 2014	December, 2019	Children and adolescents	0–19 years	Tuberculosis	18376	4661	75%
Bayleyegn et al (2021)[21]	Eastern	Ethiopia	Gondar	Cross-sectional study	January, 2020	April, 2021	Children	<15 years	Children with unemployed family, orphans, malnutrition, anaemia, and lymphopenia	253	79	100%
Berihun et al (2023)[29]	Eastern	Ethiopia	Dessie Branch	Cross-sectional study	March, 2022	June, 2022	Children	<15 years	Regimen substitution, and duration on ART <12 months	522	143	100%
Bitwale et al (2021)[31]	Eastern	Tanzania	Dodoma	Cross-sectional study	November, 2018	February, 2019	Children and adolescents	1–19 years	Tuberculosis, no HIV status disclosure, nevirapine-based regimen, orphan, poor treatment adherence, and no cotrimoxazole prophylaxis	300	102	100%
Chouraya et al (2019)[61]	Southern	Eswatini	Hhohho region	Cross-sectional study	September, 2017	October, 2018	Children	<15 years	Nevirapine-based regimen	358	79	100%
Djiyou et al (2023)[8]	Central	Cameroon	Douala	Cross-sectional study	February, 2021	September, 2021	Adolescents	10–19 years	Second-line ART regimen, baseline viral load ≥1000 copies per mL, and poor treatment adherence	279	59	100%
Elashi and van Wyk (2022)[49]	Southern	South Africa	Thabo Mofutsanyane district	Cross-sectional study	2019	2019	Adolescents	10–19 years	Low CD4 cell count, age at ART initiation, retention in care	4520	983	100%
Fataha et al (2024)[59]	Southern	Mozambique	Whole country	Cross-sectional study	January, 2019	December, 2019	Children	<15 years	Male sex, age <5 years, living outside of Maputo City, and duration on ART <6 years	33559	18671	100%

(Table continues on next page)

	Sub-region of sub-Saharan Africa	Country in which the study was conducted	Study area (city, village, or region)	Study design	Study start	Study end	Population group	Age group	Risk factors for USVL	Total number of participants included	Number of patients with USVL	JBI score
(Continued from previous page)												
Fenta et al (2021)[28]	Eastern	Ethiopia	Hawassa	Cross-sectional study	July, 2019	December, 2019	Children	<15 years	Rural, advanced WHO stage, malnutrition, baseline viral load ≥1000 copies per mL, low CD4 cell count, female, poor treatment adherence, and nevirapine-based regimen	273	113	100%
Fokam et al (2021)[45]	Central	Cameroon	Yaoundé	Cross-sectional study	December, 2018	May, 2019	Adolescents	10–19 years	Advanced clinical staging, poor treatment adherence, and NNRTI-based regimen	196	106	100%
Gachoka and Njoroge (2024)[39]	Eastern	Kenya	Nairobi	Cross-sectional study	October, 2022	October, 2022	Children	<15 years	Tuberculosis, ART side-effects, enhanced adherence counselling, no DTG-based regimen, and caregiver age <40 years	252	63	100%
Getawa et al (2021)[27]	Eastern	Ethiopia	Gondar	Cross-sectional study	March, 2017	May, 2017	Children	<15 years	Male, regimen change, being on ART for >36 months, and tuberculosis	200	25	100%
Gordon et al (2022)[7]	Eastern	Uganda	Kabale district	Cross-sectional study	September, 2019	October, 2019	Adolescents	10–19 years	Opportunistic infection, orphan, misses all meals in some days, treatment interruption, no cotrimoxazole prophylaxis, and malnutrition	249	47	100%
Isaac et al (2020)[57]	Western	Nigeria	Northern Nigeria	Cross-sectional study	December, 2017	December, 2019	Children and adolescents	0–18 years	Male, nevirapine-based regimen, and low CD4 cell count	663	340	75%
Jackson et al (2022)[52]	Southern	Zimbabwe and Malawi	Harare and Blantyre	Cohort study	2016	2019	Children and adolescents	6–19 years	Age at ART initiation >15 years, and not switching ART regimen	315	114	73%
Kabogo et al (2017)[40]	Eastern	Kenya	Nairobi	Cohort study	January, 2011	December, 2013	Children and adolescents	1–18 years	Suboptimal adherence to ART	146	64	73%
Kadima et al (2018)[37]	Eastern	Kenya	Migori and Kisumu counties	Cross-sectional study	June, 2014	May, 2015	Children	≤15 years	Malnutrition, second-line ART regimen, and male sex	1190	442	100%
Khamadi et al (2023)[32]	Eastern	Tanzania	Southern Highland zone	Cross-sectional study	January, 2019	December, 2021	Children and adolescents	1–19 years	Age <5 years, poor adherence, and attending a level 1 or 2 health facility	707	112	100%
Lorenzetti et al (2024)[60]	Southern	Mozambique	Inhambane, Maputo City, Tete, and Nampula	Corss-sectional study	October, 2020	September, 2021	Children and adolescents	0–19 years	None	12231	3338	89%
Mabizela and van Wyk (2022)[48]	Southern	South Africa	Gauteng	Cross-sectional study	January, 2015	December, 2018	Adolescents	10–19 years	Poor treatment adherence	192	50	75%
Mageda et al (2023)[10]	Eastern	Tanzania	Simiyu	Cross-sectional study	October, 2021	November, 2021	Children	2–14 years	Older age at ART initiation, and poor treatment adherence	253	17	100%
Makadzange et al (2015)[53]	Southern	Zimbabwe	Harare	Cross-sectional study	May, 2012	December, 2012	Children and adolescents	0–19 years	Age at ART initiation, and nevirapine-based regimen	599	183	100%
Mbébi Enoné et al (2023)[46]	Central	Cameroon	Littoral region	Cohort study	November, 2018	October, 2019	Children and adolescents	0–19 years	Orphan status	1029	307	82%

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	Sub-region of sub-Saharan Africa	Country in which the study was conducted	Study area (city, village, or region)	Study design	Study start	Study end	Population group	Age group	Risk factors for USVL	Total number of participants included	Number of patients with USVL	JBI score
(Continued from previous page)												
Mchomvu et al (2022)[34]	Eastern	Tanzania	Tabora region	Cohort study	January, 2018	April, 2022	Children and adolescents	0–19 years	Low CD4 cell count, second-line regimen, nevirapine-based regimen, and poor treatment adherence	378	124	82%
Mena et al (2023)[20]	Eastern	Ethiopia	Wolaita	Cohort study	January, 2017	December, 2021	Children	<15 years	Single caregiver, divorced caregiver, low CD4 cell count, and follow-up <36 months	388	42	91%
Mugo et al (2023)[56]	Western	Nigeria	Adamawa, Bauchi, Borno, Jigawa, Kano, Kebbi, Kwara, Niger, Sokoto, Yobe, and Zamfara	Cross-sectional study	April, 2019	June, 2021	Children	0–15 years	Poor treatment adherence, and being in a support group	2490	911	100%
Mukumbuta et al (2024)[66]	Southern	Zambia	Lusaka district	Cross-sectional study	July, 2021	September, 2021	Adolescents	10–19 years	Poor treatment adherence, low CD4 cell count, not sexually active, and missed clinical visits in 6 months	294	154	100%
Munyayi and van Wyk (2022)[64]	Southern	Namibia	Windhoek	Cohort study	January, 2019	December, 2021	Adolescents	10–19 years	Duration on ART <24 months, and second-line ART regime	695	78	64%
Muri et al (2017)[30]	Eastern	Tanzania	Kilombero district	Cohort study	2013	2015	Children and adolescents	<18 years	Female, low CD4 cell count, poor treatment adherence, and nevirapine-based regimen	213	54	82%
Mushy et al (2024)[36]	Eastern	Tanzania	Tanga region	Cohort study	October, 2018	April, 2022	Adolescents	10–19 years	No DTG-based regimen, dispensary facility level, and age 10–14 years	2250	226	73%
Mwangi and van Wyk (2021)[41]	Eastern	Kenya	Homa Bay County	Cross-sectional study	November, 2017	November, 2017	Adolescents	10–19 years	Poor treatment adherence, low CD4 cell count, and second-line regimen	908	182	100%
Nabukeera et al (2021)[9]	Eastern	Uganda	Kampala	Cohort study	January, 2017	March, 2019	Children	0–14 years	Advanced WHO clinical stage of HIV, ART-induced side-effects, and age <5 years	300	69	73%
Ndongo et al (2024)[43]	Central	Cameroon	Yaoundé	Cross-sectional study	December, 2021	March, 2022	Adolescents	10–19 years	Orphan, ART regimen	247	33	100%
Okonji et al (2021)[50]	Southern	South Africa	Ehlanzeni district	Cross-sectional study	September, 2002	October, 2019	Adolescents	10–19 years	Male sex, low CD4 cell count, and second-line regimen	9386	2411	100%
Onyango et al (2023)[42]	Eastern	Kenya	34 counties	Cross-sectional study	October, 2019	September, 2020	Children and adolescents	<18 years	Male sex, child's education status, caregiver sex, non-membership of a psychosocial support group, and non-membership of a voluntary savings and lending association	31 291	4404	100%
Osman et al (2020)[26]	Eastern	Ethiopia	Jimma	Cross-sectional study	April, 2019	May, 2019	Children	<15 years	Advanced WHO clinical stage of HIV	140	16	100%
Quaker et al (2024)[35]	Eastern	Tanzania	Whole country	Cross-sectional study	2018	2021	Adolescents	10–19 years	Male sex, second-line or third-line ART regimen, poor treatment adherence, attending level 1–2 health facility, and advanced WHO clinical stage of HIV	34 400	3350	100%

(Table continues on next page)

	Sub-region of sub-Saharan Africa	Country in which the study was conducted	Study area (city, village, or region)	Study design	Study start	Study end	Population group	Age group	Risk factors for USVL	Total number of participants included	Number of patients with USVL	JBI score
(Continued from previous page)												
Rwabukwisi et al (2016)[65]	Eastern	Rwanda	Kirehe and southern Kayonza districts	Cohort study	January, 2005	December, 2008	Children	<15 years	None	235	34	82%
Shiferaw et al (2019)[25]	Eastern	Ethiopia	Bahir Dar	Cross-sectional study	July, 2017	June, 2018	Children	<15 years	Nevirapine-based regimen	1567	444	100%
Shumetie et al (2021)[23]	Eastern	Ethiopia	West Gojjam zone and Amhara region	Cross-sectional study	Oct 1, 2020	Oct 15, 2020	Children	<15 years	No HIV status disclosure, advanced WHO clinical stage of HIV, enrolment viral load ≥1000 copies per mL, poor treatment adherence, and missed clinical appointment	360	76	90%
Sibhat et al (2020)[19]	Eastern	Ethiopia	Tigray	Cohort study	December, 2018	June, 2019	Children and adolescents	<18 years	Poor treatment adherence, advanced WHO clinical stage of HIV, tuberculosis, and follow-up duration	404	96	73%
Simms et al (2021)[51]	Southern	Zimbabwe	Mashonaland West, Mashonaland East, Mashonaland North, Mashonaland South, Midlands, and Masvingo	Cross-sectional study	January, 2019	March, 2019	Adolescents	10–19 years	Male sex, and no HIV status disclosure	833	292	100%
Soudebto et al (2024)[44]	Central	Cameroon	Yaoundé	Cross-sectional study	January, 2017	December, 2020	Children and adolescents	0–19 years	Rural residence	272	124	75%
Tafere et al (2023)[24]	Eastern	Ethiopia	Addis-Ababa	Cross-sectional study	July, 2021	July, 2021	Adolescents	10–19 years	ART regimen, alcohol use, cigarette-smoking, discrimination, biological mother not alive, and have a history of hospital admission in the last year	446	52	100%
Tanoh-Aka et al (2021)[62]	Western	Ivory Coast	Gbeke region	Cross-sectional study	July, 2015	December, 2019	Children	0–15 years	Malnutrition, poor treatment adherence, unschooled mother, and no prevention of vertical transmission	329	118	75%
Teasdale et al (2018)[47]	Southern	South Africa	Eastern Cape	Cohort study	2012	2015	Children	<12 years	Enrolment viral load ≥1000 copies per mL, low CD4 cell counts, and ART regimen	349	92	91%
Tsikhutsu et al (2022)[38]	Eastern	Kenya	South Rift Valley and Kisumu	Cross-sectional study	December, 2018	March, 2020	Children and adolescents	1–19 years	Duration on ART <24 months, and poor treatment adherence	935	185	100%
Tweya et al (2020)[54]	Southern	Malawi	Lilongwe	Cohort study	January, 2014	December, 2017	Children and adolescents	≤18 years	Malnutrition, nevirapine-based regimen, and male	1312	208	82%
Yiltok et al (2020)[58]	Western	Nigeria	Jos	Cross-sectional study	June, 20218	November, 2018	Adolescents	10–19 years	Poor treatment adherence	143	62	100%

ART=antiretroviral therapy. DTG=dolutegravir. JBI=Joanna Briggs Institute. NNRTI=non-nucleoside reverse transcriptase inhibitor. USVL=unsuppressed viral load.

***Table*: Studies meeting inclusion criteria**

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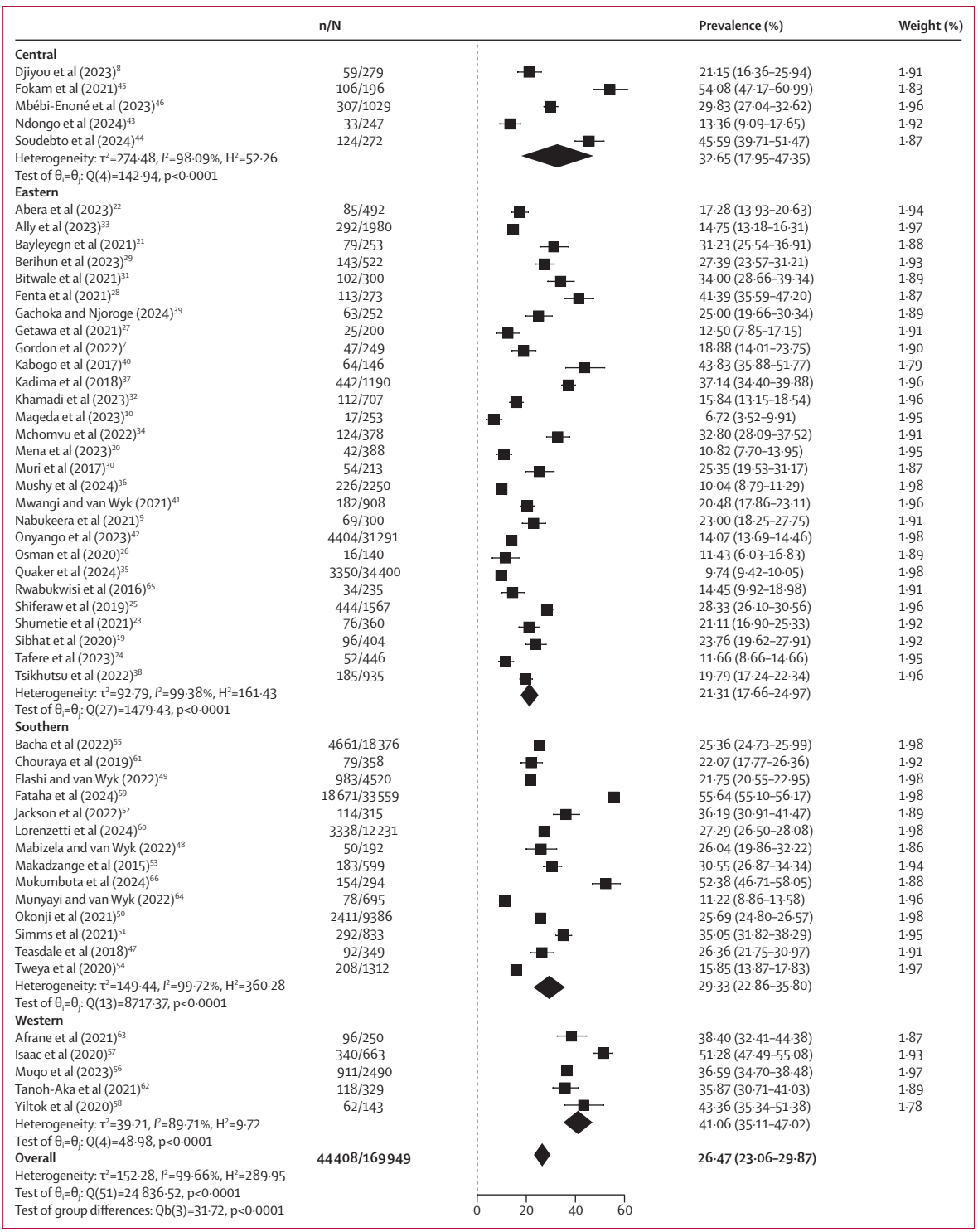

Figure 2: **Forest plot of the unsuppressed viral load prevalence among children and adolescents living with HIV in sub-Saharan Africa by sub-region**
The diamond shape represents the estimate, and the width of the diamond indicates the 95% CI.

Additionally, the analysis by study age group showed that the prevalence of unsuppressed viral load was higher in studies focusing on children (age <15 years; 26·01% [95% CI 20·51–31·51]) compared with those focusing on adolescents (age 10–19 years; 24·76 [17·36–32·16]; figure 4). Studies combining both children and

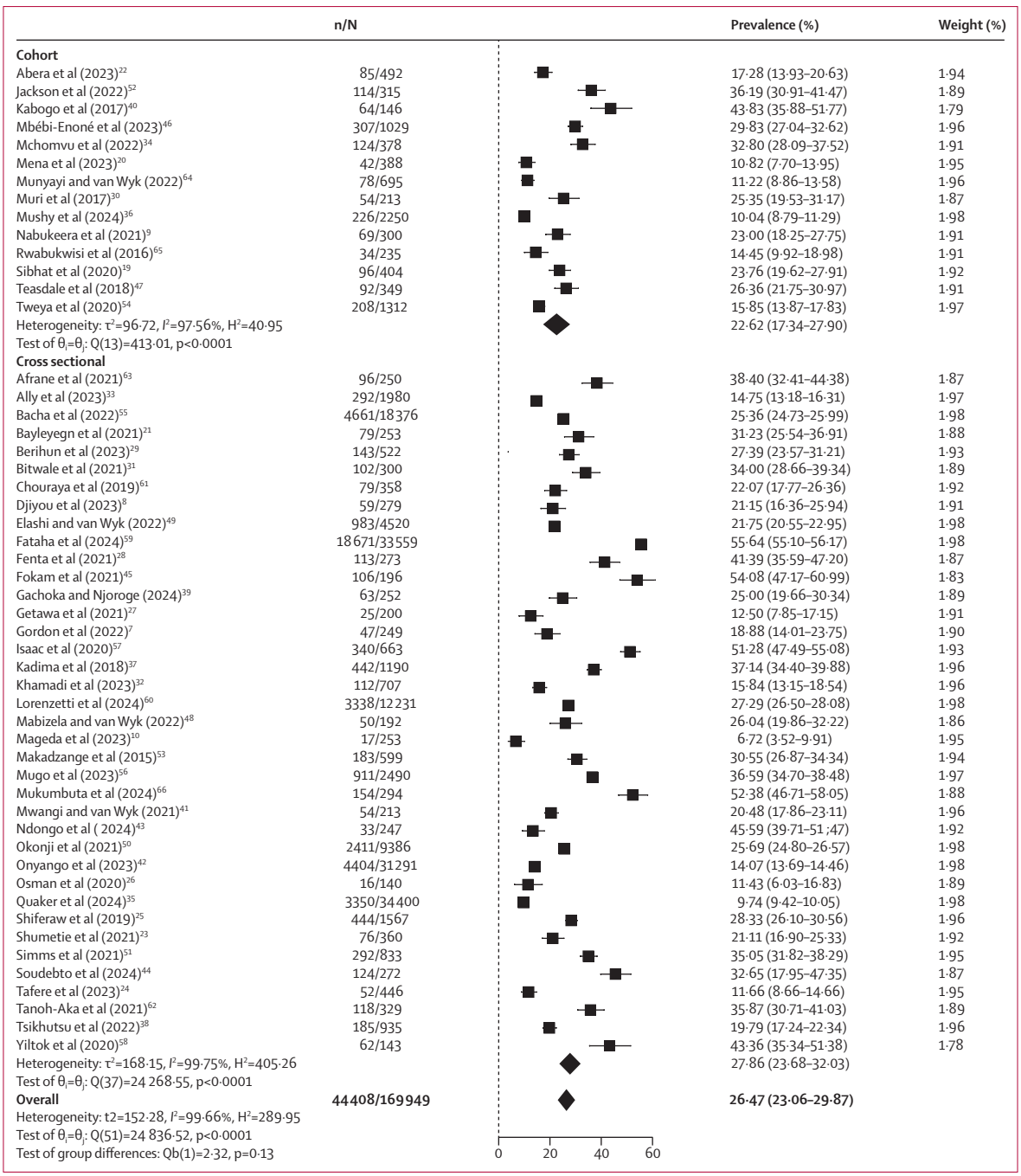

Figure 3: **Forest plot of the unsuppressed viral load prevalence among children and adolescents living with HIV in sub-Saharan Africa by study design**
The diamond shape represents the estimate, and the width of the diamond indicates the 95% CI.

adolescents (≤19 years) had the highest prevalence at 28·52% (23·33–33·72). Despite the observed variations in prevalence across age groups, the test for group differences (Q=0·79, p=0·67) showed no significant statistical variation in the prevalence rates between the three age groups.

Other factors were also associated with prevalence of unsuppressed viral load in children and adolescents on ART in sub-Saharan Africa. Sociodemographic characteristics such as younger age (<5 years),[32,33,59] rural residence,[22,44] male sex,[22,27,35,37,42,50,51,54,57,59] and orphanhood[7,21,31,43,46] were linked to a higher likelihood of unsuppressed viral load (appendix p 7). HIV care-related factors, including attending a lower-level health-care facility,[32,35,38] lack of HIV status disclosure,[23,31,33,51] and poor ART

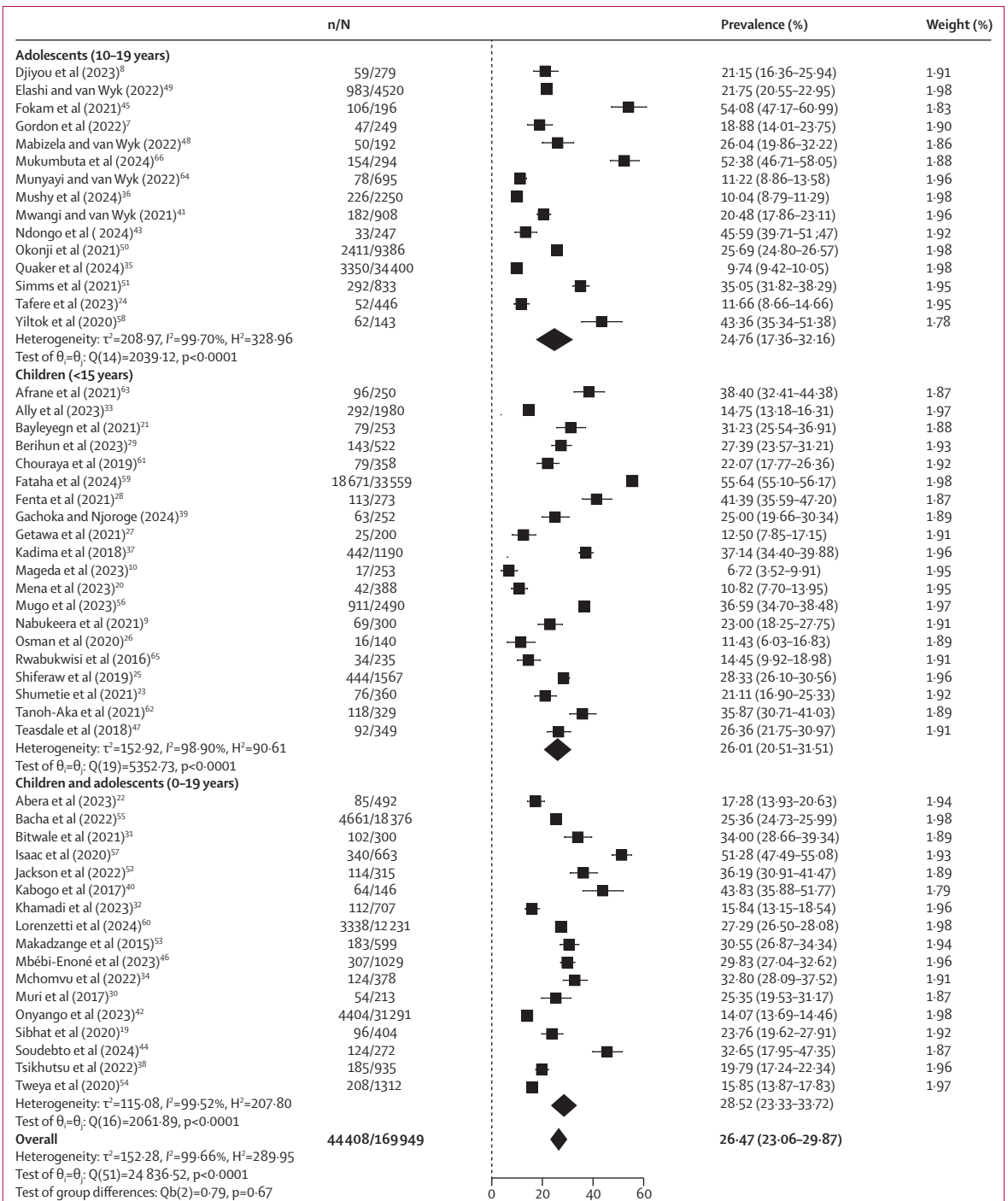

Figure 4: **Forest plot of the unsuppressed viral load prevalence among children and adolescents living with HIV in sub-Saharan Africa by age group**
The diamond shape represents the estimate, and the width of the diamond indicates the 95% CI.

adherence,[8,10,19,22,23,30–35,38,41,48,56,58,62,66] were also associated with increased risk of developing unsuppressed viral load (appendix p 8). Clinical and immunological factors, such as advanced WHO clinical stage of HIV (3–4),[9,19,22,23,26,35] low CD4 cell count,[20,22,34,41,49,50,57,63,66] malnutrition,[7,21,37,54,62] and a history of opportunistic infections[7,19,22,27,31,55,63] elevated the risk of unsuppressed viral load (appendix p 9). ART-related aspects, including absence of co-trimoxazole prophylaxis,[7,31] drug substitution history,[8,27,34,35,37,41,50,64] shorter ART duration

(<24 months),[38,64] and the use of a nevirapine-based regimen[25,30,31,34,54,57,61,63] were also significant contributors to unsuppressed viral load (appendix p 10).

Discussion

The magnitude of HIV among children and adolescents in sub-Saharan Africa is substantial, with this meta-analysis of 52 studies (169 949 children and adolescents on ART) showing a prevalence of unsuppressed viral load at 26·47% (26·01% for studies in children younger than 15 years, 24·76% for studies in adolescents aged 10–19 years, and 28·52% for studies in the combined age group). These figures, which are far below UNAIDS's 95% viral load suppression target, highlight the urgent need for targeted interventions to address this public health challenge.[4,30]

Our results show that, in studies of children alone, prevalence of unsuppressed viral load ranged from 6·72% in Simiyu (Tanzania)[10] to 55·64% in Mozambique.[59] For studies conducted among adolescents alone, the lowest prevalence recorded was 9·74% Tanzania[35] and the highest was 54·08% in Yaoundé (Cameroon).[45] Studies in children and adolescents have reported prevalences ranging from 14·07% in Kenya[42] to 51·28% in North Nigeria.[57] Differences in methodology and sample sizes used for diagnosis in individual studies conducted in each country, and differences in socioeconomic status, the quality of medical services, and geographical areas, can all have a substantial effect on the accuracy of diagnosing unsuppressed viral load. These factors could explain the observed variations in the prevalence of unsuppressed viral load in children and adolescents throughout sub-Saharan Africa. The substantial heterogeneity observed across the studies (I^2>97%, p<0·0001) indicates a complex interplay of factors affecting unsuppressed viral load, with the likelihood of considerable geographical and demographic variation. However, the lack of notable publication bias—as shown by insignificant Egger's test—strengthens the validity and dependability of our prevalence estimates.

This meta-analysis aimed to identify factors influencing unsuppressed viral load children and adolescents on ART in sub-Saharan Africa; it revealed that unsuppressed viral load linked to a range of challenges, including sociodemographic factors, HIV care management, clinical and immunological aspects, and treatment-related factors. This study further unveiled the crucial role that location of residence plays in viral load suppression. Children and adolescents inhabiting rural areas were more affected with unsuppressed viral load compared with their urban-dwelling peers. This disparity might be attributable to a confluence of factors, including (but not limited to) the low availability and accessibility of health-care services, the potentially inferior quality of health-care facilities, the shortage of clinicians with experience in HIV, and the logistical complexities associated with consistent ART distribution in rural locales.[67,68]

The study highlighted a significant correlation between young age and viral load suppression, revealing that children younger than 5 years were particularly susceptible to unsuppressed viral load. The rationale behind this trend could be multifaceted, encompassing the inherent challenges in treating of HIV in infants and toddlers, potential pharmacokinetic and pharmacodynamic considerations unique to this age group, and the inherently aggressive progression of HIV infection in early childhood.[69]

The dimension of sex emerged as a significant factor influencing viral load suppression rates. Overall, evidence indicated that male children and adolescents had a higher risk of unsuppressed viral load compared with females, similar to findings from studies in Senegal[70] and Uganda.[71] The underlying causes for such sex-based differences could be rooted in a spectrum of behavioural dynamics, varying adherence to ART protocols, and possible intrinsic biological variations in ART efficacy. The pharmacokinetics and pharmacodynamics profiles of antiretroviral medications can alter depending on a person's gender, as noted by Penot and colleagues;[72] higher concentrations of ART—which promote virological efficacy—are seen in females relative to males.[72]

Orphan status significantly influences viral load suppression rates among children and adolescents. Previous studies have shown that being a single or double orphan is linked to virological failure.[73,74] The vulnerability of children and adolescents with HIV, resulting from the loss of a biological parent or insufficient support from caregivers, exposes them to a higher likelihood of not reaching viral load suppression. The intricate combination of psychological distress, socio-economic uncertainty, and inconsistent nurturing might contribute to this elevated risk. The findings show that children and adolescents being treated at lower-tier health-care facilities (such as those classified as level 1 or 2) were found to have increased odds for presenting with unsuppressed viral load. This relationship points towards a potential disparity in the quality of care, availability of resources, and possibly the breadth of expertise available at these facilities.

Disclosure of HIV status emerges as a pivotal factor in this study. Children and adolescents who were unaware of their HIV status had a higher likelihood of treatment failure compared with those who were informed. This finding is consistent with similar results reported in Ethiopia[75] and Tanzania.[31] Disclosure is associated with several positive outcomes, including enhanced social support, stronger family cohesion, and reduced anxiety and depression levels, all of which contribute to better ART adherence, and underscoring the intricate relationship between psychological wellbeing and treatment efficacy. Ethical considerations surrounding HIV status disclosure, including timing and approach, are crucial, especially for young patients, where understanding and emotional maturity play pivotal roles.

Non-disclosure could inadvertently affect mental health and compromise treatment adherence.[76]

The most notable outcome of our analysis relates to the role of ART adherence in the context of viral load suppression. The data presented clearly show that suboptimal adherence is closely associated with unsuppressed viral load, with a 6·5-fold increase in the odds of unsuppressed viral load for those with poor adherence. Effective ART adherence is widely recognised to positively affect viral replication suppression and to improve immunological and clinical results. These advantages also help mitigate the potential risk of drug resistance.[77,78] This result is of utmost importance and highlights the crucial importance of adhering strictly to ART regimens for favourable treatment outcomes.

Our study found that advanced WHO clinical stages of HIV (3–4), opportunistic infections, low CD4 cell counts, and malnutrition significantly affect unsuppressed viral load. Advanced WHO clinical stages (3–4) are linked to unsuppressed viral load due to severe immune deterioration and significant CD4 cell depletion.[79] As HIV progresses, the destruction of CD4 cells impairs the immune system's ability to control viral replication, leading to low CD4 cell counts and high viral load.[80] Progression of HIV also complicates ART adherence and management due to increased opportunistic infections and AIDS-related complications, which further weaken the immune system and provide more targets for HIV, exacerbating viral load.[81] Poor nutritional status additionally impairs immune cell function, and affects ART absorption and efficacy, leading to ineffective viral load suppression and worsening overall health outcomes.[82]

However, the effect of delayed or missed diagnosis must also be considered as a contributing factor to the advanced stage of disease at the ART initiation, particularly in paediatric populations. Late diagnosis, as indicated by the presence of opportunistic infections and low CD4 cell counts, complicates the timely ART initiation, thus impeding the chances of sustained viral load suppression. The CHER study has emphasised the crucial importance of early ART initiation in infants and younger children, where prompt treatment is key for long-term viral load suppression.[83,84] Delayed diagnosis and subsequent late ART initiation could also explain some of the heterogeneity observed across studies, particularly in regions with poor access to health-care services and testing.

This meta-analysis found that co-trimoxazole prophylaxis, as indicated by other studies, significantly reduces the risk of unsuppressed viral load by preventing opportunistic infections in individuals with compromised immune systems. The absence of co-trimoxazole prophylaxis doubles the likelihood of unsuppressed viral load, indicating a need to investigate how co-trimoxazole boosts ART efficacy through direct antiviral effects, immune modulation, or improved adherence due to enhanced health outcomes.[85] Moreover, a patient's history of drug substitutions can reflect underlying issues such as drug resistance, erratic adherence, or metabolic variations, which can all contribute to suboptimal drug levels and inadequate viral load suppression. Additionally, ART duration plays a key role in reaching and sustaining viral load suppression in people living with HIV. Our analysis reveals that children and adolescents on ART for less than 24 months face significantly higher odds of unsuppressed viral load, highlighting the crucial nature of the early treatment phase in establishing effective viral load control. During this initial period, patients undergo physiological and psychological adjustments, necessitating targeted interventions to bolster adherence, manage side-effects, and provide comprehensive support.[86] Effective management during this phase can yield enduring benefits in viral load suppression. Despite being commonly used in resource-limited settings, nevirapine-based regimens have been linked to elevated rates of unsuppressed viral load. Research indicates that this association might stem from nevirapine's pharmacokinetic properties, resistance patterns, and its effect on the developing immune systems of children and adolescents.[53,87] Recent transitions to more efficacious regimens, such as dolutegravir-based therapies, have shown promise in improving viral load suppression, particularly in settings in which nevirapine resistance is common.[88–90] The switch to dolutegravir, which postdates many of the studies included in this review, could lead to better long-term outcomes, suggesting a potential avenue for future research. Differences in regimen types could also explain some of the heterogeneity in findings across age groups, countries, and study designs. Therefore, as countries adopt newer HIV treatment regimens, such as dolutegravir, further studies are needed to examine their effect on viral load suppression and whether they can reduce the variability observed in current studies.

These findings provide crucial insights for developing targeted interventions to improve ART outcomes in vulnerable populations, particularly in sub-Saharan Africa. Despite global efforts—such as the UNAIDS 95% viral load suppression target[4]—and renewed commitments to eradicating AIDS among paediatric and adolescent groups,[11] achieving these goals demands focused attention on younger children, rural residents, orphans, and those with advanced disease stages or opportunistic infections.

This systematic review and meta-analysis has several limitations that need to be considered when interpreting the findings. We focused exclusively on studies that used the WHO-defined threshold for viral load suppression (<1000 copies per mL)[15] to ensure consistency across the studies. The exclusion of studies using alternative viral load thresholds ensures that we did not underestimate viral load suppression rates by combining different thresholds. However, we recognise that this approach could limit the generalisability of our findings. Many of the included studies were cross-sectional, which restricts the ability to establish causal relationships between the identified factors and unsuppressed viral load.

Longitudinal studies would provide more robust evidence on the temporal relationship between these factors and viral load outcomes. Additionally, this review did not account for the varying rates of unsuppressed viral load in very young children or the effect of horizontal versus vertical transmission on viral load suppression. These factors might contribute to differential viral load suppression rates that were not fully captured in our analysis. Moreover, we observed unrealistically large OR estimates (eg, 154·50 [95% CI 33·33–716·10][48] and 209·42 [76·21–575·51];[33] figure 3, appendix p 8) in some included studies, which (along with their wide confidence intervals) suggest the presence of sparse-data bias. This bias could have carried over into the combined estimates and should be considered an important limitation of the study. The small number of studies included in some of the meta-analyses of risk factors could have led to inaccurate estimation of between-study heterogeneity. Although we used the Hartung–Knapp–Sidik–Jonkman approach and its modification for random-effects meta-analysis, which aims to provide more accurate estimates in the presence of few studies, this inaccurate heterogeneity estimation remains a limitation for our study. Despite our efforts to adjust for the confounders reported in the individual studies, unmeasured confounding factors might still be present and could potentially influence the results. Finally, we did not apply inverse probability weighting using population weights for the combined proportion (children and adolescents), which could have enhanced the precision and generalisability of the estimates. This decision was primarily due to the absence of detailed and reliable populations weights, especially those disaggregated by age group, across the included studies. As a result, application of inverse probability weighting across studies was not feasible. This limitation should be considered when interpreting the findings, as it could affect the generalisability of the results. Despite these limitations, this review provides valuable insights into the magnitude and factors associated with unsuppressed viral load among children and adolescents on ART in sub-Saharan Africa; it offers a foundation for guiding future research and intervention strategies.

Contributors

OM and KG developed the research protocol and were involved in study design, study selection, data extraction, statistical analysis, and drafting the initial version of the manuscript. YNK and SOW participated in study selection, data extraction, and quality assessment. KG and SOW served as study supervisors, contributing to the study design, preparation, and revision of the manuscript drafts, including the final draft. OM, KG, and SOW accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and were responsible for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data collected for this study are available in a Microsoft Excel file associated with this Article. This file contains the data extracted from the articles included in this systematic review. The data will be accessible from the date of publication. Interested parties can obtain the Excel file by contacting the corresponding author at the following email address: 223152330@stu.ukzn.ac.za. Access will be granted under specified conditions, and data will be shared with researchers who demonstrate a clear research objective and adhere to ethical guidelines. The study protocol is available on the PROSPERO website (CRD42023451212).

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