Global, regional, and national prevalence of HIV-1 drug resistance in treatment-naive and treatment-experienced children and adolescents: a systematic review and meta-analysis

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Summary

Background Despite significant reductions in mother-to-child HIV-1 transmission risks due to the advancements and scale-up of antiretroviral therapy (ART), the global burden of HIV-1 drug resistance (HIVDR) in treatment-naive and treatment-experienced children and adolescents remains poorly understood. In this study, we conducted a systematic review and meta-analysis to estimate the prevalence of HIVDR in these populations globally, regionally, and at the country level.

Methods We systematically searched PubMed, Embase, and Web of Science for studies reporting HIVDR in treatment-naive and treatment-experienced children and adolescents from inception to June 28, 2024. Eligible studies reported at least ten successfully genotyped cases. We excluded studies where drug resistance was not reported separately for children and adults or for treatment-naive and treatment-experienced populations. The methodological quality of eligible studies was assessed, and random-effect models were used for meta-analysis to determine the pooled overall and regimen-specific prevalence of one or more HIVDR mutations in these populations globally, regionally, or at the country level. This study is registered with PROSPERO under the number CRD42023424483.

Findings Of 2282 records identified, 136 studies (28,539 HIV-1-infected children from 52 countries) were included for analysis. The overall prevalence of HIVDR is 26.31% (95% CI, 20.76–32.25) among treatment-naive children and 74.16% (95% CI, 67.74–80.13) among treatment-experienced children (p < 0.0001). HIVDR varied widely across subregion with the highest prevalence in Southern Africa (37.80% [95% CI, 26.24–50.08]) and lowest in South America (11.79% [95% CI, 4.91–20.84]) for treatment-naive children while highest in Asia (80.85% [95% CI, 63.76–93.55]) and lowest in Europe (54.39% [95% CI, 28.61–79.03]) for treatment-experienced children. The proportion of viral failure (VF) presented positive correlation with DR prevalence for treatment-experienced children, which increased from 61.23% (95% CI, 47.98–73.72) in proportion of VF <50%–81.17% (95% CI, 71.57–89.28) in proportion of 100%. Meta-regression analysis for both groups showed that only age (naive: p = 0.0005; treated: p < 0.0001) was the sources of heterogeneity. Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistances were the most seen mutations among the treatment-naive group, with the HIVDR prevalence more than 10% in Southern Africa, Western and Central Africa, Eastern Africa, Asia, and North America. Both nucleoside reverse transcriptase inhibitor (NRTI) and NNRTI resistances were commonly seen among the treatment-experienced group, varying from 36.33% (95% CI, 11.96–64.93) in North America to 77.54% (95% CI, 62.70–89.58) in South America for NRTI and from 39.98% (95% CI, 13.47–69.97) in Europe to 68.86 (95% CI, 43.91–89.17) in Asia for NNRTI, respectively.

Interpretation This study underscores the significant burden of HIVDR among children and adolescents worldwide, particularly pronounced in sub-Saharan Africa and low-income countries. It emphasizes the critical importance of

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surveillance in all HIV-1-infected children and advocates for the adoption of dolutegravir (DTG) or other optimal formulations as first-line ART in settings where NNRTI resistance exceeds the WHO's 10% threshold. DTG's high resistance barrier, potent antiviral efficacy, and favorable safety profile makes it a superior choice for managing drug-resistant HIV-1, surpassing traditional antiretroviral therapies.

Research in context

Evidence before this study

The emergence of HIV-1 drug resistance (HIVDR) among infants, children, and adolescents poses a significant threat to global efforts in combating HIV-1/AIDS, particularly in the context of widespread implementation of a "treat all" approach and the scale-up of prevention of mother-to-child transmission programs. A comprehensive understanding of HIVDR prevalence in this vulnerable population is crucial for informing effective treatment strategies and public health policies. Prior to our study, a systematic search of PubMed, Web of Science, and Embase yielded limited evidence on the global pretreatment drug resistance (PDR) in children with HIV-1. While a meta-analysis conducted in 2016 focused on pretreatment HIVDR in children residing in sub-Saharan Africa, it lacked a comprehensive assessment of HIVDR on a global scale.

Added value of this study

Our systematic review and meta-analysis provides the most comprehensive assessment and robust evidence to date of the HIVDR prevalence in HIV-infected children worldwide. We found that the prevalence of drug resistance (DR) to non-nucleoside reverse transcriptase inhibitor (NNRTI) in treatment-naive children exceeded the WHO's 10% threshold for changing first-line antiretroviral therapy (ART) regimen in Africa, Asia, and North America, and approached this threshold in South America and Europe. Importantly, our study also sheds light on the high prevalence of both nucleoside/nucleotide reverse transcriptase inhibitor and NNRTI resistances among treatment-experienced children, with rates escalating alongside increasing proportions of viral failure.

Implications of all the available evidence

Our results show that routine HIVDR testing or at least periodic nationally representative surveys is imperative for informing the HIVDR prevalence and guiding national programmes on optimal population-level ART regimen selection. In settings where prevalence of PDR to NNRTIs exceeds 10%, or in cases of treatment failure among children on ART, timely transition to dolutegravir and other optimal formulations is paramount. We advocate for global and national support in negotiating better prices for these formulations and for facilitating smooth transitions to optimize treatment outcomes for children living with HIV-1.

Introduction

Over the past two decades, considerable progress has been achieved in expanding and sustaining prevention of mother-to-child HIV-1 transmission (PMTCT) services, as well as in scaling up care and treatment programs for children and adolescents living with HIV-1. Nevertheless, in 2022 alone, there were 130,000 new HIV-1 infections among children aged 0–14 years, with an estimated 1.54 million (IQR: 1.20 million-2.11 million) children worldwide living with HIV-1, of whom only 57% (44–78) were receiving life-saving antiretroviral therapy (ART).[1] Compounding this challenge is the emergence of antiretroviral drug resistance (DR), undermining the effectiveness of HIV-1 treatment and jeopardizing global efforts to end the AIDS epidemic in infants and children.

Infants who acquire HIV-1 during pregnancy or delivery are particularly vulnerable to AIDS or death in the first few months of life, underscoring the urgent need to address ART resistance and subsequent treatment failure to prevent unnecessary loss of life. The 2023 guidelines from the European AIDS Clinical Society (EACS) have updated the preferred and alternative first-line ART regimens for children and adolescents, emphasizing the integration of dolutegravir (DTG), an integrase inhibitor (INSTI), in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs).[2] While these updates provide expanded treatment options, it remains imperative to address the persistently high levels of pretreatment HIV-1 drug resistance (HIVDR) to non-nucleoside reverse transcriptase inhibitors (NNRTIs), particularly in resource-limited settings where access to child-friendly formulations of the most effective ART remains constrained. Moreover, the pill burden, increased vulnerability to

adverse drugs effects, and suboptimal adherence to ART contribute to the lower rates of viral load (VL) suppression among children compared to adults.[3,4]

In response to the escalating prevalence of ART resistance, WHO's Global Action Plan on HIVDR 2017–2021,[5] alongside other international initiatives, outlines crucial actions for national and global stakeholders to prevent, monitor, and respond to HIVDR. While the current recommendations place a significant emphasis on the testing of pretreatment drug resistance (PDR), particularly to NNRTIs due to their high prevalence, they also advocate for comprehensive surveillance and strategic responses to manage emerging resistance patterns across all antiretroviral drug classes, ensuring a holistic approach to addressing HIVDR on a global scale.[6] Despite Sub-Saharan Africa bearing the brunt of the pediatric HIV-1 epidemic, individual-level HIVDR testing remains prohibitively expensive and largely inaccessible in resource-limited settings. Therefore, the synthesis of globally and nationally representative HIVDR data becomes imperative for informing targeted public health interventions. To date, trends in prevalence and patterns of resistance in adult people living with HIV-1 (PLWH) have been comprehensively assessed,[7] but such systematic analysis in children and adolescents living with HIV-1 has not yet been investigated globally.

Therefore, we conducted a systematic review and meta-analysis to provide a comprehensive assessment of HIVDR among children and adolescents living with HIV-1 worldwide. Specifically, our study aims to estimate the prevalence of both pretreatment and treatment-experienced HIVDR, as well as to investigate the frequencies of drug resistance mutations of public health significance. By synthesizing available evidence, our analysis seeks to inform evidence-based interventions and guide policy efforts to optimize pediatric HIV-1 care and treatment outcomes globally.

Methods

Search strategy and selection criteria

This study constituted a systematic review and meta-regression analysis aimed at assessing the global prevalence of treatment-naive and treatment-experienced DR among children and adolescents. We conducted searches in PubMed, Web of Science, and Embase for studies published in English up to June 28, 2024. Our search strategy employed the following terms: "resistan*" AND ("`HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency syndrome") AND ("child*" OR "adolecen*" OR "infant*" OR "newborn*" OR "pediatri*"). Detailed search strategies for each database and the full list of search terms are provided in the appendix (Table S1).

We included cross-sectional, case–control, or cohort studies involving children and adolescents (aged <19 years) with or without prior ART exposure history.

Studies were eligible if they reported at least ten genotypes successfully tested using standard population sequencing methods (such as ViroSeq/TrueGene/In-house genotyping), single-genome sequencing, allele-specific real-time polymerase chain reaction (AS-PCR), and ultra-deep sequencing. Studies reporting data on PMTCT were included if they provided information on ART exposure in infants. We excluded studies that did not separately report HIVDR for children and adults or for treatment-naive and treatment-experienced populations. We include full length articles and excluded letters, meeting abstracts, case reports, case-series, comments, abstracts, notes, conference proceedings, short communications, reviews and posters due to the limited information they provided.

All titles and abstracts retrieved from the literature search were carefully examined by two independent reviewers (GLY and LYS). The same reviewers assessed the full texts of potentially eligible articles, with any disagreements resolved through consensus by two additional authors (LJY and LXR).

This systematic review and meta-analysis was conducted in accordance with The Cochrane Handbook for Systematic Reviews of Interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary PRISMA Checklist).[8] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (No. CRD42023424483).

Data extraction and quality assessment

Two main study groups, treatment-naive and treatment-experienced, were established for data extraction. Studies were categorized into one of these groups based on the ART history of PLWH. A preconceived and standardized data extraction form was utilized to collect information on various parameters, including study details (author, publication year, country/region, study design, period of sample collection, number of participants and genotypes successfully sequenced, HIV-1 subtypes, genotypic resistance sequencing assay), participant characteristics (age, sex, HIV-1 VL, US CDC or WHO clinical stage), number of patients with more than one drug-resistance mutation, with one or more NRTI/NNRTI/protease inhibitor (PI)/thymidine analogue mutation (TAM), and with multiple-class of HIVDR. We also extracted the drug resistance mutations database used to determine specific drug resistance. If an article met the inclusion criteria but had missing data, such as age and sex information, it was still included in the overall analysis. However, for specific analyses where age and sex were essential variables, those studies were excluded. Most studies reported drug-resistance mutations according to the Stanford Drug Resistance Database list,[9] while others used lists such as the WHO Surveillance Drug Resistance Mutations List,[10] the ANRS (French National Agency for

AIDS Research)[11] or the IAS-USA (International AIDS Society-USA Drug Mutation list.[12] Additionally, data on PMTCT history, prophylaxis drugs for treatment-naive individuals, antiretroviral regimen, and duration of drug exposure for treatment-experienced individuals were extracted.

We assessed the quality of the included studies using an adapted version of the risk of bias tool specifically designed for prevalence studies, as developed by Hoy et al.[13] This tool was selected due to its strong reliability and validity, having been rigorously tested and demonstrated high interrater agreement (overall Kappa statistic of 0.82). We chose this tool over the initially planned tool from our PROSPERO registration to better address the specific needs of prevalence studies, ensuring methodological rigor and the reliability of our findings. The tool addresses key domains of bias, including selection bias, measurement bias, and analysis bias, making it particularly well-suited for our systematic review. Studies were categorized as good quality (low risk of bias), fair quality (moderate risk of bias), or poor quality (high risk of bias) based on this assessment.

For studies reporting resistance data for both treatment-naive and treatment-experienced populations, multiple datasets were extracted and subjected to analysis based on ART history. In cases where studies reported characteristics and resistance mutations across multiple nations or over several sampling years, data were segmented to yield estimates tailored to individual countries and sampling years. When a study includes aggregate data from multiple regions without separate regional reporting (e.g., data on 10 out of 100 patients with inseparable resistance data from Africa and Asia), the collective results will be attributed to each involved region for regional analyses (e.g., reporting 1 resistance in 10 out of 100 patients in both Africa and Asia). Studies were categorized by region—Asia, Europe, North and South America, Eastern Africa, Southern Africa, Western and Central Africa when analyzed in regional level due to the data availability that two thirds of the datasets were from Africa (Table S4 and Fig. S1).

Statistics
The main outcome was the overall prevalence of HIV-1 ART-resistant mutations. Following an exploratory analysis, we employed Freeman-Tukey double arcsine transformation to stabilize the variances of raw prevalence data. The prevalence of ART-resistant mutations was estimated by pooling data using a random-effects model. We estimated heterogeneity between studies using Cochran's Q statistic ($p < 0.05$ indicates moderate heterogeneity) and the I^2 statistic ($\geq 50\%$ or higher indicates moderate heterogeneity). We conducted similar analyses to estimate the prevalence of drug-class-specific mutations (NRTI mutations, NNRTI, and PI) by region, as well as prevalence of selected major individual mutation within these three classes.

Subgroup analyses considered multiple variables, including country, region (Asia, Europe, North and South America, Eastern Africa, Southern Africa, Western and Central Africa), level of country income (low, lower middle, upper middle, high income), sampling year (before 2015 vs after 2015), age (≤ 2 years vs >2 years for treatment-naive participants; ≤ 7 years vs >7 years for treatment-experienced participants), PMTCT experience (yes vs no), proportion of the male ($\leq 50\%$ vs >50%) considering that the birth ratio of males to females is approximately 1:1, CD4+ T cell count (<500 vs ≥ 500 cells/mL), HIV-1 plasma VL (<5 log copies/mL vs ≥ 5 log copies/mL) given that the median VL across these studies was approximately 5 log copies/mL for both treatment-naive and treatment-experienced children, proportion of WHO Stage 3/4 or CDC stage C (<50% vs $\geq 50\%$), exposure period of antiretroviral treatment (<3 years vs ≥ 3 years), proportion of participants with viral failure (VF) (100%, 50%–99%, <50%) given the distribution of datasets number across the VF categories, ART regimen (NRTI, NRTI + NNRTI, NRTI + NNRTI/PI, NRTI + PI, NRTI + NNRTI + PI, NNRTI + PI, NRTI + NNRTI/PI/INSTI). We reanalyzed the data using datasets from 2015 onward to provide a more up-to-date and precise understanding of resistance dynamics.

Sensitivity analysis was performed by systematically omitting one study at a time to assess the stability of results and explore potential sources of heterogeneity.

Univariable and multivariable meta-regression analyses were employed to assess the impact of study and participant characteristics on the prevalence estimate. A significance level of $p < 0.05$ was utilized to determine statistical significance. The meta-regression models revealed a significant association between the age of participants and the proportion of drug-resistant mutations ($p < 0.05$). Consequently, we conducted further analyses to investigate the relationship between participant age and the prevalence of mutations in both treatment-naive and treatment-experienced children and adolescents.

Data were analyzed using the meta and metafor packages of the statistical software R, version 4.2.1.

Ethics
Ethical approval was not required for this study since it used only secondary data from existing published studies.

and had final responsibility for the decision to submit this manuscript for publication.

Results

A total of 2282 records were initially identified, of which 1100 remained after duplicate removal. After screening titles and abstracts, 714 irrelevant records were excluded. Subsequently, the full texts of 386 papers were scrutinized for eligibility, resulting in the exclusion of 250 studies. Ultimately, 136 full texts (comprising 162 datasets)[14–149] were included in the meta-analysis (Fig. 1). Among the included studies, 69 (48%) were assessed as being of good quality, while 75 (52%) were rated as fair quality; none were deemed to be of poor quality. The appendix summarizes the quality assessment and characteristics of the included studies (Tables S2 and S3). A comprehensive table outlining the Population, Intervention, Comparison, and Outcome (PICO) elements for all included studies is provided in the supplementary materials (Table S2).

In total, we analyzed 162 datasets from 136 individual reports spanning 52 countries. The study-level data encompassed 29,015 patients, of whom 16,812 individuals reporting HIVDR. A comparable number of studies reported drug resistance data for treatment-naive and treatment-experienced individuals across regions, with the majority of data originating from Africa (10,951/16,812, 65.1%, Table 1). The median age was 6 months (IQR 3.62–36.9) for treatment-naive children and 94.8 months (IQR 60.0–121.5) for treated children. Approximately 64.4% (47/73) of datasets involving treatment-naive drug resistance experienced PMTCT. Among treated individuals, approximately 55.2% (8323/15,090) experienced VF during ART, with the therapy duration ranging from 1995 to 2024 and a median duration of 26.5 months (IQR 12.7–50.1, Table 1).

We present overall and subgroup analyses on the prevalence of one or more drug-resistance mutations among treatment-naive and treatment-experienced children across various characteristics (Tables 2 and 3). The overall HIVDR prevalence is 26.31% (95% CI, 20.76–32.25) among treatment-naive children and 74.16% (95% CI, 67.74–80.13) among treatment-experienced children (p < 0.0001) (Fig. S2). HIVDR prevalence varied widely across subregions, with the highest prevalence in Southern Africa (37.80% [95% CI, 26.24–50.08]) and the lowest in South America (11.79% [95% CI, 4.91–20.84]) for treatment-naive children; it was highest in Asia (80.85% [95% CI, 63.76–93.55]) and lowest in Europe (54.39% [95% CI, 28.61–79.03]) for treatment-experienced children. By country, HIVDR prevalence was highest in Haiti (71.38% [95% CI, 65.94–76.40]) and lowest in Mali and Benin (0% [95% CI, 0.00–8.04]) for treatment-naive children; it was highest in Belgium and Puerto Rico (100% [95% CI, 96.90–100.00]) and lowest in Mexico and Portugal

(3.70% [95% CI, 0.45–12.75]) for treatment-experienced children (Fig. 2). Sensitivity analysis indicated that the main summary prevalence did not significantly change among treatment-naive and treatment-experienced HIV-1-infected children (Fig. S3).

The PDR tended to decline with an increase in World Bank income level among treatment-naive children, with low-income countries showing a PDR prevalence of 33.89% (95% CI, 19.15–50.33) and high-income countries showing a PDR prevalence of 21.07% (95% CI, 10.81–33.45) (Table 2). However, among treated patients, upper-middle-income countries exhibited the highest DR prevalence of 85.03% (95% CI, 76.51–92.00) (Table 3, Table S6). HIVDR prevalence decrease over the sampling years (naive: 27.04% [95% CI, 20.95–33.56] before 2015 vs. 25.40% [95% CI, 11.80–41.79] after 2015; treated: 75.42% [95% CI, 67.66–82.46] before 2015 vs. 67.93% [95% CI, 55.59–79.15] after 2015), while no significant differences in resistance prevalence across different sampling times were observed (both p values > 0.05). The results of the subgroup analyses conducted using datasets from 2015 onward are presented in the appendix (Table S5).

Children exclusively exposed to NRTI regimens showed the highest DR prevalence of 84.53% (95% CI, 75.12–92.14). Additionally, a positive correlation was observed between the proportion of VF and DR prevalence, increasing from 61.23% (95% CI, 47.98–73.72) when VF was less than 50% to 81.17% (95% CI, 71.57–89.28) when VF was 100% (Tables 2 and 3).

Considerable heterogeneity was observed between HIVDR prevalence estimates; therefore, we did a meta regression to explore sources of variation. Univariate random-effects meta-regression analyses indicated that region (p = 0.0319), history of PMTCT (p = 0.0045), and age (p = 0.0001) could be potential sources of heterogeneity among treatment-naive children, while no significant differences were observed in sampling year (p = 0.1352), income level (p = 0.4238), or CD4 count (p = 0.6686). Among treated patients, univariate random-effects meta-regression analyses revealed that age (p = 0.0198) and VF (p = 0.0307) could be a source of heterogeneity. Multivariate random-effects meta-regression analysis for both groups indicated that only age (naive: p = 0.0005; treated: p ≤ 0.0001) constituted a source of heterogeneity (Table S6). Thus, we analyzed associations between age and HIVDR prevalence for treatment-naive and treatment-experienced HIV-1-infected children. We found that PDR prevalence declined with increasing age among treatment-naive children, ranging from 35.39% (95% CI, 28.11–43.00) in children under 2 years to 14.48% (95% CI, 8.68–21.34) in those aged 2 years and older. In contrast, a positive correlation between HIVDR and age persisted in the treated group, ranging from 60.54% (95% CI, 49.58–71.01) in children under 7 years to 81.80% (95% CI, 74.48–88.17) in those aged 7 years and older (Tables 2 and 3 and Fig. 3).
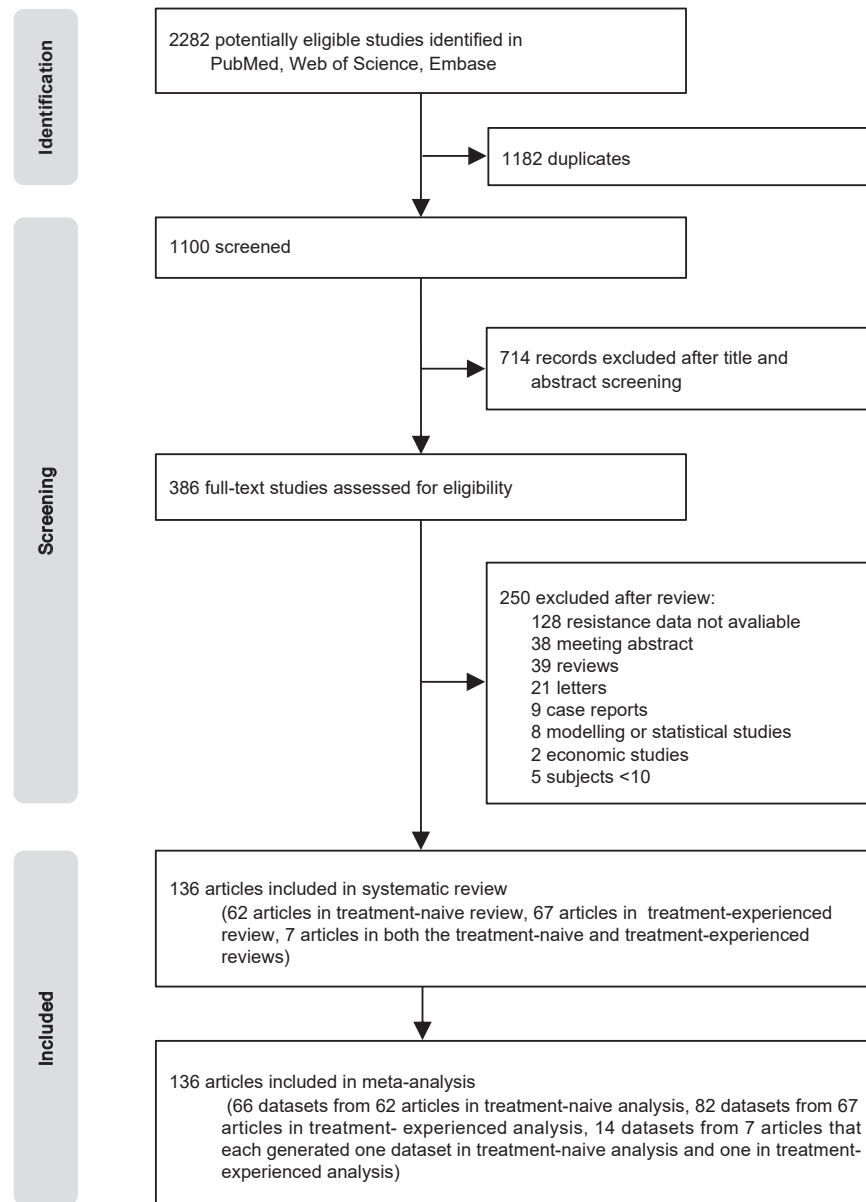
Fig. 1: PRISMA Flowchart for study selection.

Regarding the class of ART drugs, NNRTI resistances were the most commonly observed mutations among the treatment-naive group, occurring in 23.64% (95% CI, 18.26–29.45) of patients with one or more drug-resistance mutations. Southern Africa exhibiting the highest PDR prevalence at 36.57% (95% CI, 24.94–49.01), followed by Eastern Africa (27.03%, [95% CI, 14.85–41.16]), while Europe had the lowest PDR at 6.95% (95% CI, 2.34–13.39). For NNRTI resistance, the most common mutation observed was Y181 C/F/G/I/S/V with a PDR prevalence of 16.01% (95% CI, 11.20–21.45), followed by K103 N/S at 11.56% (95% CI, 8.82–14.59) (Fig. 3 and

Fig. S4). Given the mutations potentially associated with rilpivirine (RPV), the PDR prevalence is 7.72% (95% CI, 5.51–10.23) for K101P, 16.66% (95% CI, 12.42–21.35) for Y181I/V, and 5.02% (95% CI, 3.49–6.78) for Y188L.

NRTI resistances were the most commonly observed mutations among the treatment-experienced group, occurring in 65.19% (95% CI, 58.48–71.62) of patients with one or more drug-resistance mutations, with Asia exhibiting the highest DR prevalence of 76.23% (95% CI, 58.24–90.47) and North America the lowest DR prevalence of 36.33% (95% CI, 11.96–64.93). For NRTI resistance, the most common mutation observed was

Region	Number of datasets	Number of patients	Number of genotypes	Sampling year[a]	Age (months)[a]	PMTCT experience (number of datasets)	Proportion of viral failure (%)[a]	ART treatment time (years)[a]	Regime (%)
Treatment-naive									
Eastern Africa	12	1182	975	2008 (2000–2018)	6.0 (1.4–108.0)	8	NA	NA	NA
Southern Africa	19	4956	2610	2008 (2002–2017)	4.7 (1.2–25.2)	15	NA	NA	NA
Western and Central Africa	10	933	898	2014 (2006–2019)	44.4 (3–76.8)	6	NA	NA	NA
Asia	10	1250	893	2008 (2002–2019)	21.0 (0.7–144.0)	6	NA	NA	NA
South America	8	715	580	2009 (2002–2013)	21.5 (2.3–108)	5	NA	NA	NA
North America	8	4018	747	2003 (1998–2013)	5.5 (2.6–180)	4	NA	NA	NA
Europe	6	871	783	2001 (1995–2012)	6.0 (1.0–26)	3	NA	NA	NA
Treatment-experienced									
Eastern Africa	18	4220	2163	2010 (2003–2020)	66.0 (6–144)	NA	53.8	2.2 (0.8–5.0)	NRTI + NNRTI (66.6) NRTI + NNRTI/PI (16.6) NRTI (11.1) NNRTI + PI (5.5)
Southern Africa	19	5424	3425	2009 (2004–2018)	94.8 (7.3–154.8)	NA	45.8	2.9 (1.0–7.6)	NRTI + NNRTI/PI (33.3) NRTI + NNRTI (26.6) NRTI + PI (20.0) NRTI (13.3) NRTI + NNRTI + PI (6.6)
Western and Central Africa	17	1776	880	2012 (2001–2021)	84.0 (4.2–192)	NA	60.9	2.3 (0.5–9.8)	NRTI + NNRTI/PI (41.1) NRTI + NNRTI (23.5) NRTI (11.7) NRTI + NNRTI + PI (23.5)
Asia	13	2056	1494	2010 (2004–2024)	96.0 (36–166.8)	NA	66.5	2.0 (0.1–3.9)	NRTI + NNRTI (53.8) NRTI + NNRTI/PI (46.1)
South America	6	412	403	2006 (1999–2018)	85.2 (7.6–144)	NA	93.7	2.5 (1.7–11.0)	NRTI + NNRTI + PI (33.3) NRTI + NNRTI/PI (16.6) NRTI (16.6) NRTI + PI (16.6) NRTI + NNRTI (16.6)
North America	8	563	447	2007 (2001–2015)	85.2 (7.6–144)	NA	58.7	0.9 (0.5–10.1)	NRTI + NNRTI/PI (50.0) NRTI + NNRTI (25.0) NRTI + PI (25.0)
Europe	8	639	514	2002 (1999–2020)	111.0 (2.5–182.4)	NA	63.1	2.1 (2.1–1.9)	NRTI + PI (40.0) NRTI + NNRTI/PI (20.0) NRTI + NNRT + PI (20.0) NRTI + NNRTI/PI/INSTI (20.0)

NA, not applicable; ART, antiretroviral therapy; PMTCT, the prevention of mother-to-child transmission; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase inhibitor. Several datasets are generated from the same study. If multiple regions are involved in the study, statistics will be repeated. 16 datasets out of 8 studies were included in both treatment-naive and treatment-experienced datasets; 12 datasets out of 4 studies were included in treatment-experienced datasets; 18 datasets out of 7 studies were included in treatment-naive datasets; 45 datasets out of 20 studies were included in total. Statistics for the treatment-naive group (6 datasets) and the treatment-experienced group (4 datasets) were repeated to the presence of multiple regions. [a]Median (range).

Table 1: Characteristics of included studies, by region.

M184V/I, with a DR prevalence of 45.40% (95% CI, 36.63–54.31). It is worth noting that NNRTI DR prevalence were also high, ranging from 39.98% to 68.86% across various regions in the treatment-experienced group. The top two mutations were consistent with those observed in the treatment-naive group (Fig. 4 and Fig. S5).

Regarding PI, the most prevalent mutations among the treatment-naive group were I84A/C/V (5.00%, [95% CI, 1.04–13.92]) and D30N (2.27%, [95% CI, 0.00–7.02]);

for the treatment-experienced, the most common mutation was D30N, observed in 9.65% (95% CI, 2.59–19.90) of cases (Fig. S6). INSTI drug resistance was observed in the treatment-experienced group across 13 datasets, with an overall prevalence of 2.82% (95% CI, 0.75–5.80). The highest prevalence was reported in South America, at 6.45% (95% CI, 0.12–15.70). The most common INSTI mutation was R263K, with a prevalence of 3.79% (95% CI, 0.49–9.09) (Fig. 4 and Fig. S7).

	Number of datasets	Number of HIV-infected individuals	Number of individuals with DR	Prevalence of DR (95% Confidence Interval)	Heterogeneity		p value for subgroup difference
					I^2	p value	
Overall	73	6914	2464	26.31% (20.76–32.25)	96%	0	
Region[a]							<0.01
South America	8	580	91	11.79% (4.91–20.84)	84%	<0.01	
North America	8	747	435	34.21% (15.35–55.93)	97%	<0.01	
Europe	6	783	83	14.31% (7.19–23.19)	83%	<0.01	
Asia	10	893	140	18.30% (7.32–32.32)	95%	<0.01	
Eastern Africa	12	975	268	31.35% (18.40–45.98)	94%	<0.01	
Southern Africa	19	2610	1144	37.80% (26.24–50.08)	95%	<0.01	
Western and Central Africa	10	898	366	21.60% (8.44–38.26)	95%	<0.01	
World Bank Income Level							0.44
Low income	15	1218	421	33.89% (19.15–50.33)	97%	<0.01	
Lower middle income	20	1539	663	30.14% (19.35–42.07)	96%	<0.01	
Upper middle income	17	1532	463	22.8% (14.47–32.28)	93%	<0.01	
High income	11	730	252	21.07% (10.81–33.45)	97%	<0.01	
Age group (years)							<0.01
<2	44	4398	1984	35.39% (28.11–43.00)	94%	<0.01	
≥2	29	2516	480	14.48% (8.68–21.34)	95%	<0.01	
Sampling Year							0.86
<2015	62	5943	2103	27.04% (20.95–33.56)	97%	<0.01	
≥2015	11	971	361	25.40% (11.80–41.79)	94%	<0.01	
PMTCT experience							<0.01
Yes	50	4818	2014	32.58% (25.18–40.42)	96%	<0.01	
No	23	2031	450	16.52% (10.26–23.82)	96%	<0.01	
Proportion of male							0.19
< 50%	23	4024	1593	28.71% (19.52–38.84)	97%	<0.01	
≥50%	14	1000	186	18.97% (9.75–30.21)	93%	<0.01	
HIV plasma viral load ($\log_{10}$ copies/mL)[a]							0.16
<5	9	672	314	33.59% (17.61–51.65)	97%	<0.01	
≥5	18	1676	265	19.73% (11.1–29.95)	93%	<0.01	
Proportion of WHO Stage 3/4 or CDC stage C							0.67
<50%	6	563	101	16.93% (10.68–24.20)	76%	<0.01	
≥50%	4	728	127	14.61% (5.57–26.85)	95%	<0.01	

CDC, National Centers for Disease Control; DR, drug resistance; PMTCT, the prevention of mother-to-child transmission; WHO, World Health Organization. Several datasets are generated from the same study. [a]The median extracted from the original literature was used for grouping.

Table 2: **Pooled prevalence of HIV-1 drug resistance among treatment-naive children.**

The most prevalent drug resistance among dual-therapy were NRTI + PI among the treatment-naive group (13.51% [95% CI, 0.00–50.17]) and NRTI + NNRTI in the treatment-experienced group (46.55% [95% CI, 36.22–57.03]) (Fig. S8). Regarding triple class therapy, the drug resistance prevalence were 0.94% (95% CI, 0.00–4.04) among the treatment-naive group and 6.69% (95% CI, 3.67–10.39) among the treatment-experienced group (Table S3).

Discussion

Our findings indicate that drug resistance both in treatment-naive and treatment-experienced children and adolescents has become a worldwide is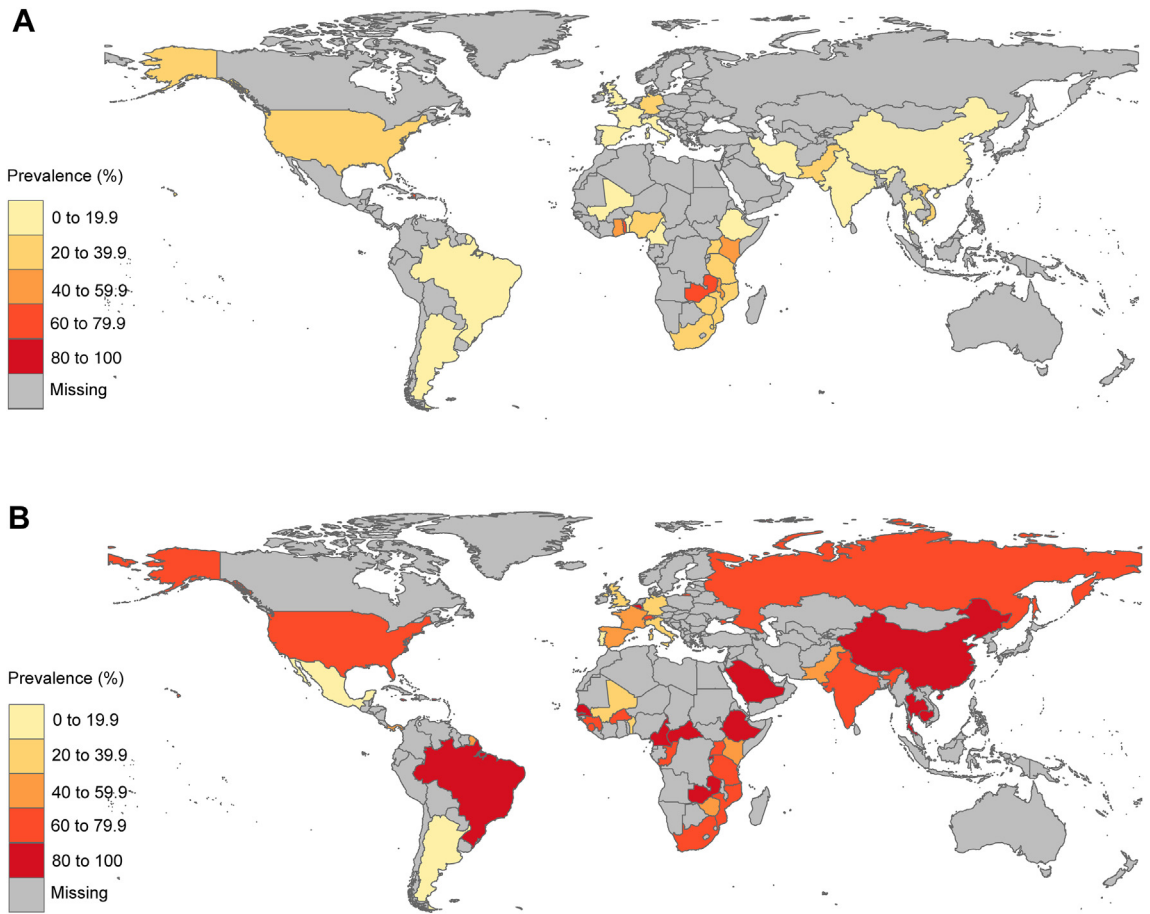sue, with the overall HIVDR prevalence being 26.31% among treatment-naive children and 74.16% among treatment-experienced children. Drug resistance in treatment-naive children is primarily concentrated in Southern Africa, East Africa, Central and West Africa, and North America, predominantly due to NNRTI mutations. Children younger than 2 years or received PMTCT exhibited higher PDR. Furthermore, the drug resistance among treatment-experienced children was more severe, with higher DR prevalence in various regions involving regimens of NRTI, NNRTI, and PI. Children older than 7 years or those who experienced VF had higher post-treatment DR prevalence. The different epidemics of drug resistance in treatment-naive and treatment-experienced children underscore the need for targeted decision-making in developing effective strategies to monitor for, prevent and respond to the emergence of HIVDR.

	Number of datasets	Number of HIV-infected individuals	Number of Individuals with DR	Prevalence of DR (95% Confidence Interval)	Heterogeneity		p value for subgroup difference
					I^2	p value	
Overall	89	7656	5256	74.16% (67.74–80.13)	97%	0	
Region							0.63
South America	6	403	274	75.72% (53.81–92.37)	96%	<0.01	
North America	8	447	258	56.88% (27.45–83.98)	98%	<0.01	
Europe	8	514	273	54.39% (28.61–79.03)	96%	<0.01	
Asia	13	1494	982	80.85% (63.76–93.55)	98%	<0.01	
Eastern Africa	18	2163	1189	68.68% (54.83–81.09)	96%	<0.01	
Southern Africa	19	3425	2366	69.68% (53.17–84.02)	99%	<0.01	
Western and Central Africa	17	880	618	72.02% (58.23–84.04)	95%	<0.01	
Income level							0.17
Low income	18	1258	868	75.70% (60.91–88.03)	98%	<0.01	
Lower middle income	24	1776	1160	72.24% (61.77–81.66)	96%	<0.01	
Upper middle income	22	2679	2181	85.03% (76.51–92.00)	96%	<0.01	
High income	11	649	415	70.20% (50.92–86.51)	96%	<0.01	
Age group (years)							<0.01
<7	33	3223	1657	60.54% (49.58–71.01)	96%	<0.01	
≥7	45	4076	3360	81.80% (74.48–88.17)	96%	<0.01	
Sampling Year							0.30
<2015	61	5089	3448	75.42% (67.66–82.46)	97%	<0.01	
≥2015	20	2644	1808	67.93% (55.59–79.15)	97%	<0.01	
Proportion of male							0.10
<50%	20	2222	1253	65.52% (51.32–78.49)	97%	<0.01	
≥50%	52	4791	3686	78.17% (70.89–84.71)	96%	<0.01	
CD4 cell count (cells/mL)[a]							0.66
<500	18	998	768	73.63% (56.27–88.01)	96%	<0.01	
≥500	18	1066	800	78.2% (63.95–89.79)	96%	<0.01	
HIV plasma viral load ($\log_{10}$ copies/mL)[a]							0.37
<5	24	2208	1762	78.71% (67.16–88.41)	95%	<0.01	
≥5	17	2034	1146	69.45% (51.03–85.23)	98%	<0.01	
Proportion of WHO Stage 3/4 or CDC stage C							0.54
<50%	18	1609	1102	75.27% (61.45–86.94)	97%	<0.01	
≥50%	17	1902	1040	69.38% (53.81–83.07)	97%	<0.01	
Antiretroviral treatment time (years)							0.44
<3	46	3570	2338	70.88% (61.52–79.46)	97%	<0.01	
≥3	26	2770	1790	76.38% (64.75–86.37)	97%	<0.01	
Proportion of viral failure							0.05
100%	28	3318	2278	81.17% (71.57–89.28)	97%	<0.01	
50%–99%	15	1379	1109	73.16% (61.73–83.29)	92%	<0.01	
< 50%	28	2097	1229	61.23% (47.98–73.72)	98%	<0.01	
ART regimen[b]							<0.01
NRTI	7	636	575	84.53% (75.12–92.14)	85%	<0.01	
NRTI + NNRTI	30	3292	2010	73.54% (60.80–84.63)	98%	<0.01	
NRTI + NNRTI/PI	24	2636	1977	78.09% (70.47–84.90)	95%	<0.01	
NRTI + PI	9	336	206	66.06% (36.83–90.17)	97%	<0.01	
NRTI + NNRTI + PI	8	516	308	61.14% (32.40–86.32)	97%	<0.01	
NNRTI + PI	1	199	93	73.96% (64.00–82.38)			
NRTI + NNRTI/PI/INSTI	1	96	71	73.60% (66.95–79.78)			

CDC, National Centers for Disease Control; DR, drug resistance; PMTCT, the prevention of mother-to-child transmission; WHO, World Health Organization; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase inhibitor. Several datasets are generated from the same study. [a]The median extracted from the original literature was used for grouping. [b]ART regimes are defined as the maximum proportion of all treatment among each dataset.

Table 3: **Pooled prevalence of HIV-1 drug resistance among treatment-experienced children.**

A

Prevalence (%)
- 0 to 19.9
- 20 to 39.9
- 40 to 59.9
- 60 to 79.9
- 80 to 100
- Missing

B

Prevalence (%)
- 0 to 19.9
- 20 to 39.9
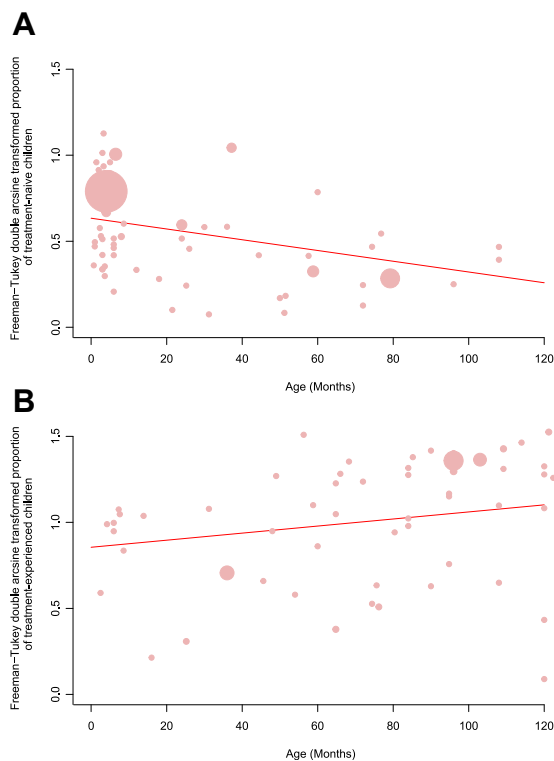- 40 to 59.9
- 60 to 79.9
- 80 to 100
- Missing

Fig. 2: Prevalence of HIV-1 drug resistance among treatment-naive children (A) and treatment-experienced children (B) by countries. Global distribution of HIV-1 drug resistant prevalence demonstrated by different color. The gray area represents countries with unavailable resistance data.

The risk of HIV-1 transmission to infant substantially decreases when mother receives ART during pregnancy and delivery, along with ART given to the infant postpartum.[150] However, an unintended consequence of ART use for PMTCT is the potential development of drug resistance in a small number of infected infants. HIVDR in infants and children with perinatal HIV-1 infection may stem from either a drug-resistant strain transmitted from the mother, or the administration of pediatric ART or ART used for PMTCT, or maternal ART.[151] This study revealed that children who underwent PMTCT exhibited a higher PDR (32.58%) compared to those who did not (16.52%), indicating that prior ART drug exposure is a significant risk factor for pretreatment HIVDR. The 2010 WHO guidelines on PMTCT recommended a preferred first-line ART regimen during pregnancy, consisting of an AZT + 3TC backbone combined with an NNRTI, along with daily administration of NVP or twice-daily AZT to infants from birth or as soon as possible thereafter until 4–6

weeks of age. Most studies included in our analysis adhered to these recommendations, resulting in a notable prevalence of NNRTI and NRTI drug resistance across various regions.

The 2016 WHO consolidated ART guidelines recommended that countries where PDR to NNRTIs exceeds 10% among individuals starting first-line ART should promptly consider alternative regimens without NNRTIs. Our analysis revealed that NNRTI DR prevalence exceeded 10% in Southern Africa, Western and Central Africa, Eastern Africa, and North America. A mathematical model projected that in sub-Saharan Africa, where NNRTI DR prevalence surpasses 10% and NNRTI-based ART remains the first-line option, this resistance could contribute to a cumulative 16% increase in AIDS-related deaths (890,000 deaths) and a 9% rise in new HIV-1 infections (450,000) over the next 15 years.[152] Conversely, PI-based second-line ART remains a viable option for treatment-naive children, with PDR for PIs remaining below 10% across various regions.

A

B

Fig. 3: Prevalence of HIV-1 resistance among treatment-naive children (A) and treatment-experienced children (B) to any drug mutations by age of sampling. Each bubble represents a study and the size of the bubble is proportional to the size of the study. The trend line is predicted prevalence.

However, access to PI-based regimens remains limited, with less than 5% of ART recipients in most LMICs receiving them. Moreover, the cost of second-line regimens in LMICs averages three times higher than first-line regimens, amounting to US$ 263 per patient per year compared to US$ 85.[153]

The development of HIVDR in children on ART is commonly associated with factors such as poor adherence, utilization of suboptimal regimens, and issues related to drug absorption or pharmacokinetics.[154] These factors contribute to subtherapeutic drug levels and the rebound of viremia with resistant viruses. Given that most included studies focused on treatment-experienced children with varying degrees of treatment failure, the DR prevalence ranged from 54.39% to 80.85% across various regions. Notably, even among children from studies with a proportion of VF less than 50%, the pooled prevalence of HIVDR remained high at 61.23%. HIVDR in treatment-experienced children necessitates more expensive second-line regimens, increasing costs associated with further transmission of highly resistant and potentially untreatable viruses. The WHO estimated that when DR prevalence to NNRTI reaches 10%, an additional 2510 individuals per 100,000

starting ART fail to achieve and maintain VL suppression below 1000 copies/mL, requiring second-line ART. This translates to an annual increase of US$ 502,000 for the purchase of second-line drugs per 100,000 people initiating ART.[6] It is noteworthy that DR prevalence for NNRTI and NRTI in children on ART exceeded 20% in each region. As a prominent member of the NNRTI class, RPV has garnered significant attention not only for its role in contemporary treatment regimens but also for the potential application of its long-acting formulation, which has been increasingly advocated for use in adolescents. Our findings reveal that the DR prevalence associated with RPV in treatment-experienced children is notably elevated for the Y181I/V mutation, with a prevalence of 16.66%. This observation is particularly critical in regions with high levels of NNRTI resistance, where the availability of alternative therapeutic options may be constrained. Furthermore, the DR prevalence for PI was over 10% in each region except for the Eastern Africa in our analysis. Particularly striking was the finding that dual DR prevalence to NNRTIs and NRTIs was observed in 46.55% of treatment-experienced children, highlighting the limited availability of alternative regimens.

In 2019, WHO updated interim guidelines recommending DTG in combination with a NRTI backbone as the preferred first-line regimen for infants and children with approved DTG dosing. A raltegravir (RAL)-based regimen may be suggested as an alternative first-line option for infants and children lacking access to approved DTG dosing, and for neonates, a RAL-based regimen may be the preferred first-line choice.[155] Compared to efavirenz (EFV)-based regimens, mathematical modeling predicts that initiating first-line ART with DTG would increase the prevalence of VL suppression (from a mean of 77% to 86%), reduce mortality (from 4.5 to 3.5 persons per 1000 person-years), and decrease HIV-1 incidence (from 0.79 to 0.72 new HIV-1 infections per 100 person-years).[156] This modeling also suggests that in sub-Saharan Africa and similar settings where the cost of a DTG-containing regimen is comparable to that of an EFV-based regimen, adopting DTG as the first-line treatment would be cost-effective and could potentially lead to cost savings. Therefore, reducing the prices of new first-line drugs like DTG or RAL, as well as second-line drugs such as PI, could prove to be a promising and cost-effective strategy in combating drug resistance in children.[6]

Despite global HIV-1 treatment guidelines recommending DTG-based ART for first-, second-, and third-line treatment as the most promising strategy to mitigate increasing drug resistance levels, fewer than half of sites in low- and middle-income countries had fully implemented or planned to implement these recommendations.[155] On World AIDS Day, UNAIDS and CHAI announced a groundbreaking agreement that achieved a significant 75% reduction in the cost of HIV-
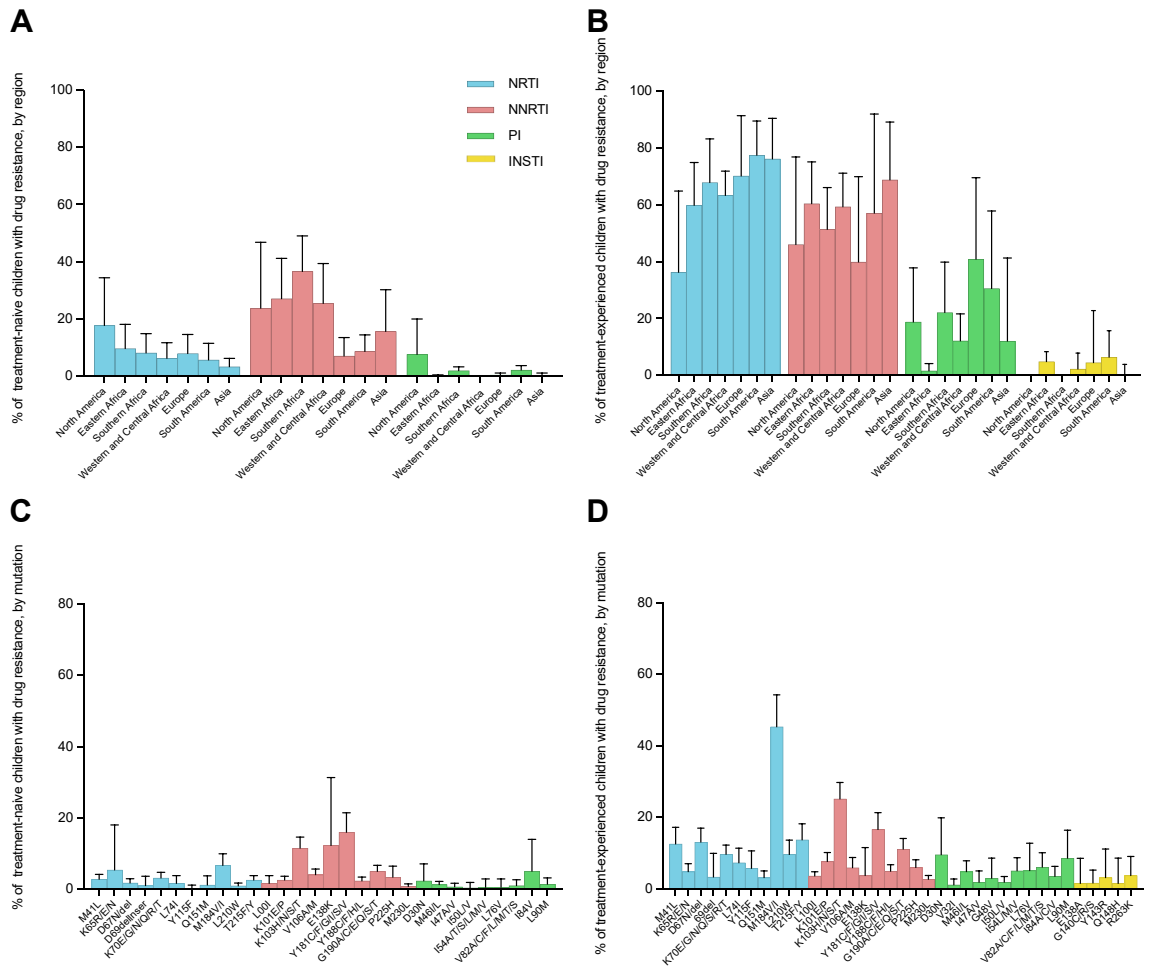
Fig. 4: Prevalence of drug-resistance mutations in children with any mutation stratified by region and drug class. Pooled estimation with 95% confidence interval error bars of NRTI (blue), NNRTI (red), PI (green) and INSTI (yellow) resistance prevalence of treatment-naive (A and C) and treatment-experienced (B and D) children. NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase inhibitor.

1 treatment for children in low- and middle-income countries. This agreement ensured that DTG 10 mg dispersible tablets would be available at a cost of US$ 4.50 for a 90-count bottle.[157] This development makes the WHO-recommended, preferred first-line DTG-based antiretroviral treatment more accessible in affordable and child-friendly generic formulations for young children and infants as young as four weeks of age, weighing more than 3 kg. A rapid transition to this optimal treatment regimen, coupled with improved HIV-1 diagnosis and other supportive measures, is crucial to urgently reduce the 95,000 preventable AIDS-related deaths in children.[158] Therefore, prior to wide-spread use of DTG in children, early monitoring of HIVDR is essential to prevent its development. Since HIVDR testing is not routinely offered to all individuals starting ART in most low- and middle-income countries,

periodic nationally representative surveys are the gold standard to inform the DR prevalence and guide a country's choice of recommended regimens for first-line ART. Furthermore, WHO-recommended ART site-based HIVDR early warning indicators (EWIs) could be employed to prevent the emergence of HIVDR.[159,160] These indicators include ART prescribing practices, rates of loss to follow-up, patient retention on first-line ART, adherence to on-time drug pick-up, attendance of on-time ART clinic appointments, and continuity of ART drug supply.

Our study has several limitations that warrant consideration. Firstly, our search strategy was limited to articles published in English, potentially overlooking relevant studies published in other languages. More-over, the geographical distribution of the included studies was skewed, with a predominant focus on the

African region and less representation from South America, North America, Europe, and Asia. This discrepancy in geographic coverage might affect the overall representativeness of our findings. Additionally, some including studies conducted at non-national levels introduces the possibility of bias in estimating national resistance rates. Furthermore, the use of various genotyping methods across the included studies poses a challenge in standardizing the data for meta-analysis, potentially affecting the accuracy of our results. Despite attempts to explore sources of heterogeneity through meta-analyses, considerable unexplained heterogeneity persisted, potentially limiting our ability to accurately identify specific epidemic trends. Lastly, our study may not fully capture the resistance prevalence in treatment-experienced children with a high proportion of VF, thereby limiting the generalizability of our findings to the broader population of children undergoing treatment. In settings where drug resistance surveillance is unfeasible, conducting nationally representative surveys is recommended to assess whether resistance rates surpass established thresholds, thereby guiding adjustments to first-line regimens.

In conclusion, our global meta-analysis highlights the significant burden of HIVDR among both treatment-naive and treatment-experienced HIV-1-infected children and adolescents, especially in sub-Saharan Africa and low-income countries. The prevalence of PDR to NNRTIs exceeded the critical threshold of 10% across the entire Africa region and approached 10% in Europe and South America. These findings underscore the urgent need for a comprehensive, co-ordinated, and integrated approach to address HIVDR. Implementing routine HIVDR testing or conducting periodic nationally representative surveys is crucial for accurately assessing the DR prevalence and informing national programs on the optimal selection of population-level ART regimens. In regions where DR prevalence to NNRTIs exceeds 10% or in cases of treatment failure among children on ART therapy, prioritizing the transition to DTG and other optimal formulations is imperative. Efforts to facilitate this transition, including guidance on the best practices for transitioning to optimal formulations and advocating for improved pricing through negotiation, should receive robust support at both global and national levels. Collaboration among key stakeholders, including countries, non-governmental organizations, PLWH and their communities, civil society organizations, United Nations programs and agencies, and international implementing partners and donors, is essential in achieving these objectives.

Contributors
JL conceptualized and supervised the study. JL, LG, LS, FB and DS designed the study. JL, LG and LS designed study search terms. JL, LG, DS and FB identified studies for inclusion. LG, YL, XL and YH collected data. LG, YL, XL and YH extracted data and assessed data quality. JL, LG, YL and XL analyzed or interpreted data. JL and LG drafted the manuscript. YL, XL and YH have verified the underlying data. All authors critically reviewed or revised the manuscript and approved the final version of the manuscript.

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Declaration of interests
All authors declare no competing interests.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102859.

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