Safety and efficacy of abacavir for treating infants, children, and adolescents living with HIV: a systematic review and meta-analysis

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Summary

Background Abacavir is a nucleoside reverse transcriptase inhibitor recommended in paediatric HIV care. We assessed the safety and efficacy profile of abacavir used in first, second, or subsequent lines of treatment for infants, children, and adolescents living with HIV to inform 2021 WHO paediatric ART recommendations.

Methods In this systematic review and meta-analysis, we included observational and experimental studies conducted in infants aged 0–1 year, children aged 1–10 years, and adolescents aged 10–19 years living with HIV; with data on safety or efficacy, or both, of abacavir-based antiretroviral therapy (ART). Published in English or French between Jan 1, 2009, and Oct 1, 2020, plus an updated search to incorporate studies published between Oct 1, 2020, and May 15, 2022. Studies could be non-randomised or non-comparative and include patients who are treatment-naive or those who previously received abacavir (only if abacavir was combined with other ART). Case studies, studies in adults aged 18 years or older, and those assessing the effect of maternal ART exposure were excluded. We extracted data related to study identifier, study design, study period, setting, population characteristics, ART treatment, and safety (any hypersensitivity reaction, death, grade 3 or 4 adverse events, treatment discontinuation, any other morbidities, and serious adverse events), and efficacy outcomes (HIV viral load and CD4 counts reported at 6 and 12 months after ART initiation). Using random-effect models, we estimated weighted pooled incidence and relative risk (RR) of outcomes. The protocol is published in PROSPERO (CRD42022309230).

Findings Of 1777 records identified, 1475 (83%) were screened after removing duplicates and a further 1421 (96%) were excluded. Of 54 full-text articles assessed for eligibility, 33 (61%) were excluded. Four records were identified from grey literature plus one duplicate from database searching, resulting in 24 studies included (two randomised controlled trials, one single-arm trial, 13 prospective cohorts, seven retrospective cohorts, and two cross-sectional studies). 19 studies described safety data and 15 described efficacy data. 18 (75%) studies were conducted in ART-naive participants. The risk of bias was considered moderate to high for most studies, and all outcomes had significant between-study heterogeneity. Data from 24 265 participants were included, of whom 7236 (30%) received abacavir. Abacavir hypersensitivity reaction was reported in nine (38%) studies, with an incidence ranging from 0.00% to 8.26% (I²=88%; p<0.0001). The incidence of death (reported in seven studies) following abacavir treatment varied from 0.00% to 5.49% (I²=92%; p<0.0001) and from 57% to 78% at 12 months (I²=85%; p<0.0001). Viral suppression (<400 copies per mL) varied from 50% to 70% at 6 months (P=92%, p<0.0001) and from 57% to 78% at 12 months (P=88%, p<0.0001).

Interpretation Toxic effects due to abacavir use remain rare and manageable. Despite scarce data on efficacy, this meta-analysis supports the use of abacavir as a preferred first-line regimen for infants and children living with HIV.

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Introduction

In 2020, 2.8 million children and adolescents aged 19 years or younger were living with HIV worldwide, with more than 90% in sub-Saharan Africa. Despite improvements in antiretroviral therapy (ART) accessibility in resource-limited settings in the past 15 years, ART coverage remains suboptimal and a lower proportion of children receive ART (54% vs 74% adults). Abacavir is a nucleoside reverse transcriptase inhibitor that has progressively replaced stavudine (d4T) due to fewer toxic effects, such as lipodystrophy and metabolic abnormalities. Abacavir is also preferred to tenofovir
Abacavir can be safely used among infants, children, and adolescents living with HIV, with a focus on the past decade. Our results confirmed that abacavir toxicity remains rare and manageable in this population. Abacavir efficacy compared with other drugs remains unclear, with lower efficacy observed in some cohorts than seen in randomised clinical trials. These findings should be interpreted with caution because the results are highly heterogeneous between the included studies.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we included observational and experimental studies conducted in infants aged 0–1 year, children aged 1–10 years, and adolescents aged 10–19 years living with HIV, with data on safety or efficacy, or both, of abacavir use in first, second, or subsequent lines of treatment for infants, children, and adolescents living with HIV to inform 2021 WHO paediatric ART recommendations.
adolescents (appendix pp 1–4). We searched grey literature sources for patient-level data or summary estimates by hand screening reference lists of systematic reviews, international guidelines on HIV treatment, clinical trial registries, and targeted conference abstracts published between January, 2018 and March, 2022 (appendix p 5). Study authors were contacted when further clarification was needed.

Titles, abstracts, and the full text were independently screened by two reviewers (JJ and VL), with technical support using the Rayyan web app. Main reasons for exclusion during the full text review stage were documented (appendix pp 6–8). Discordance was resolved by discussions with the project team. This systematic review and meta-analysis is an update of a previous review15 published in 2016 regarding the safety outcomes, and here, we include new results on efficacy outcomes. The protocol is published in PROSPERO (CRD42022309230).

Data analysis
We extracted data related to study identifier, study design, study period, setting, population characteristics (sex and age groups), ART treatment (comparative groups and whether patients previously received ART treatment), and safety and efficacy outcomes (using a piloted data extraction spreadsheet). Data extraction was done by a single unmasked reviewer (JJ) and checked and validated independently by a second reviewer (VL). Endnote software (version X9.2) and the Rayyan web app were used to identify and exclude duplicate data. Reported safety outcomes were any hypersensitivity reaction, death, grade 3 or 4 adverse events, treatment discontinuation, any other morbidities, and serious adverse events (defined as any life-threatening adverse event or reaction that requires hospitalisation, results in persistent or substantial disability or incapacity, or any other important medical condition). Efficacy outcomes extracted were HIV viral load (expressed as virological suppression using a threshold of 400 or 50 copies per mL or as other viral load outcomes if not expressed as a threshold) and CD4 counts (expressed in cell counts or percentages); both commonly reported at 6 and 12 months after ART initiation.

The quality of scientific research and overall risk of bias were assessed using the Cochrane risk of bias tool (version 2.0) for randomised controlled trials (RCTs), the 2013 US National Institutes of Health quality assessment tool for non-randomised interventional studies, and Clarity’s clinical advances using the research and information translation tool for observational studies.

Safety and efficacy outcomes according to abacavir exposure were first described within a narrative synthesis and pooled incidences were then estimated with 95% CIs using a meta-analysis with a random-effect model and building forest plots. Heterogeneity between studies was assessed by quantifying the inconsistency between incidence rate estimates with Q, χ², and I² tests calculated using MetaXL software (version 5.3; EpiGear International, Sunrise Beach, QL, Australia). Only analyses with an I² of 90% or less are displayed using forest plots. Relative risk of safety and efficacy outcomes between the abacavir-containing regimen group (intervention group) and non-abacavir-containing regimen group (control group) were summarised by risk ratio (RR) and 95% CI using DerSimonian and Laird random-effect models and building forest plots. Heterogeneity between risk ratio was assessed using the τ² statistic and calculated with Review Manager (version 5.4; Cochrane Collaboration, Copenhagen, Denmark).

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

Of 1777 records identified through database searching, 1475 (83%) were screened after removing duplicates and a further 1421 (96%) were excluded after title and abstract screening (figure 1). Of 54 full-text articles assessed for eligibility, 33 (61%) were excluded. Three records were identified from grey literature plus one duplicate from database searching and other sources.

| Country                  | Study period | Study design and follow-up | Patients receiving abacavir | ART regimen of comparison group | Previous ART treatment and duration | Median or mean patient age at baseline | Breakdown by sex |
|--------------------------|--------------|----------------------------|-----------------------------|---------------------------------|------------------------------------|---------------------------------------|-----------------|
| Mulenga et al (2016)     | Zambia and Uganda 2010-11 | Open-label, parallel-group, multi-arm trial (CHAPAS-3); 96 weeks | 164 (34%) of 478 | Stavudine (n=156) versus zidovudine (n=158) versus abacavir; backbone of lamivudine and either nevirapine or efavirenz | ART naive (76%) versus previously received ART (24%); stavudine for >2 years with viral load <50 copies per mL | Median age 2.6 years (IQR 1.6–4.0) for ART-naive patients versus 6.2 years (5.5–7.2) for those who previously received ART | 49% male and 51% female ART naive; 52% male and 48% female previously received ART |
| Dirajlal-Fargo et al (2017) | Uganda 2010-11 | Sub-study nested within the CHAPAS-3 trial; 48 weeks | 41 (35%) of 118 | Stavudine (n=42) versus zidovudine (n=35) versus abacavir; backbone of lamivudine and either nevirapine or efavirenz | ART naive | Median age 2.8 years (IQR 1.7–4.3) | 49% male and 51% female |
| Strehlau et al (2018)    | South Africa 2010-13 | Unblinded open-label RCT; 56 weeks (in children with viral suppression without lipodystrophy) | 107 (50%) of 213 substituted from stavudine to abacavir | Previously received ART (mean duration 3.5 years [SD 0.26] for abacavir vs 3.3 years [0.8] for stavudine) | Mean age 4.2 years (SD 1.0) for patients receiving abacavir versus 4.3 years (0.9) for those receiving stavudine | 47% male and 53% female |
| Fortuny et al (2014)     | North America, Europe, and South Africa 2004-10 | Phase 2, open-label, multicentre, single-arm trial; 48 weeks | 109 (100%) of 109 | Fosamprenavir, with ritonavir (n=70) or without ritonavir (n=39); abacavir used as backbone, no comparison group | ART naive (38%), previously received ART and were protease inhibitor-naive (26%), previously received ART and protease inhibitor (37%) | Median age 9.5 years (IQR 2-18) | 47% male and 53% female |
| Technau et al (2014)     | South Africa 1998-2013 | Prospective cohort, 15 months | 1536 (16%) of 9543 | Stavudine (n=8007) versus abacavir, backbone of lamivudine and either efavirenz or ritonavir-boosted lopinavir | ART naive | Median age 7 months (IQR 4-18) for patients receiving ritonavir-boosted (lopinavir based) and 96 months (63-129; efavirenz based) | 50% male and 50% female |
| Fortuin de Smidt et al (2017) | South Africa 2004-14 | Prospective cohort; median 41.0 months (IQR 14-72) | 1043 (29%) of 3579 | Lamivudine-stavudine plus either efavirenz (most common regimen used) in children younger than 3 years (n=1193) or ritonavir-boosted lopinavir in those older than 3 years (n=842) | ART naive | Median age 64 months (IQR 23-89) | 50% male and 50% female |
| de Waal et al (2020)     | South Africa 2006-17 | Prospective cohort, median 15.0 months (IQR 4-2-36 2) for abacavir and 10.6 months (IQR 2.5-25.6) for zidovudine 10 6 | 931 (73%) of 1275 | Zidovudine | ART naive | Median age 67 days (IQR 48-80) for abacavir and 32 days (6-66) for zidovudine | 44% male and 56% female |
| Patel et al (2012)       | USA 1993-2007 | Prospective cohort, median 5.5 years | 789 (26%) of 3035 | Abacavir versus no abacavir | ART naive (17%) versus previously received ART (83%) | 44% of patients aged 5 years or younger | 49% male and 51% female |
| Patel et al (2014)       | USA 2007-09 | Prospective cohort, 4 years | 46 (28%) of 165 | Abacavir versus no abacavir | Previously received ART (median duration 11.0 years [IQR 7.7-12.5] vs 0.0 years [0.0-3.3] for abacavir) | Median age 16.7 years (IQR 15.9-17.9) | 49% male and 51% female |
| Tadesse et al (2019)     | Ethiopia 2017-19 | Prospective cohort, 48 weeks | 37 (33%) of 111 | Lamivudine-efavirenz plus either zidovudine (n=15), abacavir (n=37), or tenofovir disoproxil fumarate (n=59) | ART naive | Median age 5.9 years (IQR 5-12) | 47% male and 53% female |

(Table 1 continues on next page)
| Country                  | Study period | Study design and follow-up | Patients receiving abacavir | ART regimen of comparison group | Previous ART treatment and duration | Median or mean patient age at baseline | Breakdown by sex               |
|-------------------------|--------------|----------------------------|-----------------------------|---------------------------------|-----------------------------------|--------------------------------------|----------------------------------|
| Nahirya-Ntege et al    | 2007-10      | Prospective cohort, nested within the ARROW trial; range 3-5-5 years | 1150 (100%) of 1150         | All children received ABC and lamivudine plus nevirapine or efavirenz and those in the induction-maintenance groups also received zidovudine | ART naive                         | Age ranged from 3 months to 17 years (median 6 years) | 50% male and 50% female        |
| Crichton et al         | 2000-16      | Prospective cohort; median 4-6 years (IQR 1.5-9.0; outcomes at 12 months) | 139 (100%) of 139           | No comparison group; abacavir-lamivudine plus either ritonavir-boosted lopinavir (n=54), zidovudine and nevirapine (n=45), or nevirapine (n=19); other (n=21) | ART naive                         | Median age 62 days (IQR 35-78)   | 40% male and 60% female         |
| Pareek et al           | 2015-16      | Prospective cohort; 12 months | 48 (100%) of 48             | No comparison group; abacavir with lamivudine plus nevirapine (n=32) or abacavir with lamivudine plus efavirenz (n=16) | ART naive                         | Mean age 9-8 years (SD 3.4)       | 75% male and 25% female          |
| Manglaniet al          | 2013-14      | Prospective cohort; 12 months (study period) | 100 (100%) of 100           | No comparison group             | Abacavir taken for a median of 7 days (range 3-15) in those who were to receive ABC (n=90) and 88 days (15-77) in those who were receiving ABC (n=10) | ART naive                         | Median age 11 years (range 2-18) | 61% male and 39% female          |
| Chakravarty et al      | 2013-14      | Prospective cohort; 12 months | 101 (100%) of 101           | No comparison group             | ART naive                         | Mean age 5-8 years (SD 3.5)       | 70% male and 30% female          |
| Cassim et al           | 2005-13      | Retrospective case-control; 12 months | 57 (33%) of 171             | Stavudine versus abacavir; backbone of lamivudine and ritonavir-boosted lopinavir | ART naive                         | Median age 3-11 months (IQR 1.98-6.05) | 43% male and 57% female         |
| Technau et al          | 2004-11      | Retrospective cohort; 12 months | 402 (20%) of 2036           | Stavudine (n=163) versus abacavir; backbone of lamivudine plus either efavirenz (n=26) in the stavudine group vs n=210 in the abacavir group or ritonavir-boosted lopinavir (n=672 vs n=192) | ART naive                         | Median age 10 months (IQR 4-20) for ritonavir-boosted (lopinavir based) and 86 months (60-113); efavirenz based | 50% male and 50% female         |
| Frange et al           | 2000-09      | Retrospective cohort; median 26 months (IQR 18-72) during ritonavir-boosted lopinavir treatment | 19 (44%) of 43              | Ritonavir-boosted lopinavir with backbone lamivudine (n=36), zidovudine (n=26), stavudine (n=5), or abacavir (n=19) | ART naive                         | Median age 4 years (IQR 1.8-8.0) | 60% male and 40% female          |
| Langs-Barlow et al     | 2004-11      | Retrospective cohort; no follow-up information | 44 (11%) of 403             | Comparison group (abacavir exposure yes or no); most common regimen of zidovudine (n=327) plus lamivudine (n=331) and either efavirenz (n=250) or nevirapine (n=331) | Both ART naive (8%) and previously received ART (82%) | Mean age 10-8 months (SD 4-14) for ART naive patients and 87-3 months (SD 40-7) for those who previously received ART | 44% male and 56% female ART naive; 52% male and 48% female previously received ART |
| Mega et al             | 2014-17      | Retrospective cohort; 42 months | 87 (49%) of 179             | Zidovudine plus lamivudine and either efavirenz or ritonavir-boosted lopinavir or nevirapine | Previously received ART for at least 6 months | Mean age 6-53 years (SD 2-83) | 45% male and 55% female          |

(Table 1 continues on next page)
including one cohort nested in an RCT. Seven (29%) of 24 studies were conducted in ART-naive participants. Four (17%) studies were multi-cohort studies including one cohort nested in an RCT. Seven (29%) were retrospective cohort studies and two (8%) were cross-sectional surveys. These studies were conducted in various settings; nine (38%) in southern Africa (Zambia, South Africa, and Zimbabwe), six (25%) in eastern Africa (Ethiopia, Uganda, and Malawi), two (8%) in western Africa (Ghana and Nigeria), three (13%) in south Asia (India), three (13%) in Europe, and three (13%) in North America. Four (17%) studies were multi-regional. The study period ranged from 1998 to 2019, and eleven (46%) studies started in 2010 or later. Follow-up varied from 48 weeks to more than 5 years. Median age ranged from 32 days (IQR 6–66) to 17 years (IQR 16–18) at inclusion. Six (25%) studies included infants younger than 12 months and eight (33%) included adolescents aged 10 years or older at baseline (table 1).

The two comparative RCTs were classified as low risk of bias, whereas the single-arm trial was classified as moderate risk. Of 21 observational studies, one (5%) was classified as low risk of bias and eight (40%) as moderate or unclear risk of bias. 12 (60%) were classified as high risk mainly because of the retrospective study design, which reduces confidence in exposure and outcome assessments (appendix pp 9–10).

Regarding the safety outcomes (table 2), abacavir hypersensitivity reaction was reported in nine studies (38%; one RCT, one single-arm trial, and seven prospective cohorts) with an incidence ranging from 0.00% to 8.26% and a significant between-study heterogeneity ($I^2=85%$; $p<0.0001$; figure 2A). The RCT by Mulenga and colleagues compared hypersensitivity reactions by drug regimen and reported an incidence of two (1%) of 164 for the abacavir group, five (3%) of 156 for the stavudine group, and one (1%) of 158 for the abacavir group, five (3%) of 156

### Table 1: Characteristics of included studies on abacavir safety and efficacy

| Country         | Study period | Study design and follow-up | Patients receiving abacavir | ART regimen of comparison group                                                                 | Previous ART treatment and duration | Median or mean patient age at baseline | Breakdown by sex |
|-----------------|--------------|----------------------------|-----------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------------|------------------|
| Ethiopia        | 2015–17 Retrospective cohort, 42 months | 87 (49%) of 179 | Zidovudine plus lamivudine and either efavirenz or ritonavir-boosted lopinavir or nevirapine | Previously received ART for at least 6 months | Mean age 6.53 years (SD 2.83) | 45% male and 55% female |
| Nigeria         | 2008–10 Retrospective cohort, 42 months | 31 (39%) of 80 | At enrolment: zidovudine plus nevirapine (n=74), efavirenz (n=5), or abacavir and ritonavir-boosted lopinavir (n=1); change in ART regimen (n=33, including n=31 with abacavir) | ART naive | Median 3.0 years (IQR 1.1–6.0) | 43% male and 57% female |
| South Africa    | 2014–15 Cross-sectional | 231 (46%) of 501 | Several different regimen including abacavir, lamivudine, and efavirenz (n=165) or tenofovir disoproxil fumarate, emtricitabine, and efavirenz (n=115) | Previously received ART for 5 years (IQR 2–10) | Median age 14 years (IQR 12–16) | 46% male and 54% female |
| Malawi          | 2018–19 Cross-sectional | 32 (4%) of 806 | No information on regimen; nucleoside reverse transcriptase inhibitor zidovudine (n=630) or tenofovir disoproxil fumarate (n=142) plus efavirenz, ritonavir-boosted lopinavir, or nevirapine | Previously received ART for at least 6 months | Median age 10 years (IQR 7–13) | 53% male and 47% female |

ART=antiretroviral therapy. RCT=randomised controlled trial.
| Age group                  | Control group               | Hypersensitivity reactions | Grade 3 or 4 adverse events | Mortality | Treatment discontinuation | Morbidities and adverse events |
|---------------------------|-----------------------------|-----------------------------|----------------------------|-----------|---------------------------|--------------------------------|
| Mulenga et al (2016)\(^a\) | Children Stavudine and zidovudine | Abacavir (two [1%]) versus stavudine (five [3%]) and zidovudine (one [1%]) | Abacavir (51 [31%]) versus stavudine (46 [29%]) and zidovudine (53 [34%]) | Abacavir (nine [5%]) versus stavudine (seven [4%]) and zidovudine (three [2%]) | NA | Primary endpoint (ie, grade 2 or greater clinical adverse event or confirmed grade 3 or grade 4 laboratory adverse event; 54% with abacavir vs 67% with stavudine vs 65% with zidovudine), lipodystrophy (0% vs 1% vs 0%), and mitochondrial disease (1% vs 1% vs 0%) |
| Dirajl-Fargo et al (2017)\(^a\) | Children Stavudine and zidovudine | NA | NA | NA | NA | Median change in Homeostatic model assessment of insulin resistance at 48 weeks (6% [QR –34% to 124%] vs 14% [–29% to 0%] vs 22% [−30% to 69%] with stavudine) |
| Strehlau et al (2018)\(^a\) | Children Stavudine | NA | NA | 0 | NA | Lipodystrophy (five [5%] vs 17 [16%] with stavudine), mean weight-for-age Z score (−0·1% vs −2·7% vs −0·6% with zidovudine) |
| Fortuny et al (2014)\(^a\) | Children and adolescents | NA | Abacavir (nine [8%]) | Abacavir (22 [32%]) | NA | At least one adverse event (42 [39%] with abacavir) |
| Fortuin-de Smidt et al (2017)\(^a\) | Children and adolescents | Lamivudine and stavudine plus efavirenz or ritonavir-boosted lopinavir (most common) | Abacavir (two [4%] vs not reported for control) | NA | Abacavir (58, 30 cases [95% CI 23–39] per 1000 patient-years) versus control (84, 87 cases [81–93] per 1000 patient-years) | Treatment-limiting toxicity (three, 1.6 cases [95% CI 0.5–4.8] per 1000 patient-years with abacavir vs 0.01, 0.0 cases [0.0–0.0] per 1000 patient-years with control) |
| de Waal et al (2020)\(^a\) | Infants Zidovudine | Abacavir (one [4%] vs not reported for control) | NA | NA | 12-month treatment discontinuation; abacavir (61 [8%] of 783) versus control (HR 0.16 [95% CI 0.10–0.23]) | NA |
| Patel et al (2012)\(^a\) | Children Abacavir versus no abacavir | NA | NA | NA | NA | Incident cardiomyopathy (eight [8%] with abacavir vs 91 [92%] with no abacavir, adjusted OR 0.7 [95% CI 0.3–1.5]) |
| Patel et al (2014)\(^a\) | Adolescents Abacavir versus no abacavir | NA | NA | NA | NA | Abdominal aorta: Pathobiological Determinants of Atherosclerosis in Youth score of 0 (29 [23%]) or ≥1 (17 [44%]), with current use of abacavir (adjusted OR 1.8 [95% CI 0.6–5.3]) |
| Nahirya-Ntege et al (2011)\(^a\) | Infants, children, and adolescents | Abacavir (four [1%]) | Abacavir (46 [4%]) | Abacavir (seven [13%] of 52) | Abacavir side-effects included fever (eight [16%]); skin rash (seven [14%]); respiratory (six [12%]), gastrointestinal (two [4%]), and constitutional (one [2%]) symptoms |
| Crichton et al (2020)\(^a\) | Infants | Abacavir (one [1%]) | Abacavir (eight [6%] within the first 7 days of ART) | NA | Due to ART safety (four of 139, cumulative incidence 3.6% [95% CI 1.4–7.8]) and for any reason (35 of 139, cumulative incidence 11.8% [7.3–18.9]) at 12 months with abacavir | NA |
| Pareek et al (2019)\(^a\) | Children and adolescents | Abacavir (none [0%]) | Abacavir (one [2%]) not related to abacavir hypersensitivity reaction | NA | Abacavir side-effects included fever (eight [16%]); skin rash (seven [14%]); respiratory (six [12%]), gastrointestinal (two [4%]), and constitutional (one [2%]) symptoms |
| Manglani et al (2018)\(^a\) | Children and adolescents | Abacavir (two [2%]; both HLA-B*5701 positive) | NA | NA | NA | NA |

(Table 2 continues on next page)
related to cotrimoxazole, and no deaths were reported. In the prospective cohort study by Chakravarty and colleagues, 32 eight (8%) of 101 children who received abacavir developed a clinically diagnosed hypersensitivity reaction and symptoms resolved after stopping abacavir in all children. Of these eight children, four with concomitant illness were HLA-B*5701 negative and two carried the HLA-B*5701 allele. The other six studies reported low rates of hypersensitivity reactions (all lower than 2%).

All-cause treatment discontinuation was reported in one RCT 21 and four prospective cohorts, 23,24,28,29 with an incidence ranging from 1% to 14% and significant between-study heterogeneity ($I^2$=97%; $p<0·001$; table 2).

Five studies 32,33,37,38,39 described adverse events such as skin rash, pneumonia, or gastrointestinal symptoms. Two studies 23,28 specifically reported grade 3 or 4 adverse events. In the RCT by Mulenga and colleagues, 38 917 (835 clinical and 40 laboratory) grade 2–4 clinical or grade 3–4 laboratory adverse events occurred in 104 (67%) of 156 children receiving stavudine, 103 (65%) of 158 receiving zidovudine, and 105 (64%) of 164 receiving abacavir (hazard ratio [HR] 0·99 [95% CI 0·75–1·29];

### Table 2: Safety outcomes in children and adolescents receiving an abacavir-containing regimen

| Age group | Control group | Hypersensitivity reactions | Grade 3 or 4 adverse events | Mortality | Treatment discontinuation | Morbidities and adverse events |
|-----------|--------------|---------------------------|-----------------------------|-----------|---------------------------|-------------------------------|
| Chakravarty et al (2016) 32 | Children | NA | Abacavir (eight [8%]; two HLA-B*5701 positive) | NA | NA | NA | One had a febrile illness, two had skin infections, and two had concomitant pulmonary tuberculosis; all symptoms resolved after stopping abacavir |
| Cassim et al (2017) 33 | Infants | Stavudine | NA | Abacavir (two [4%] versus control (nine [8%])) | NA | NA | Median weight-for-age Z score at 6 months (-0.93 [IQR -1.42 to 0.03] with abacavir vs -1.18 [-1.95 to 0.03] with control; $p=0.18$) and at 12 months (-0.70 [-1.25 to 0.17] vs -0.64 [-1.44 to 0.22]; $p=0.93$); and median height-for-age Z score at 6 months (-1.65 [-2.41 to -0.67] with abacavir vs -1.58 [-2.65 to -0.74] with control; $p=0.67$) and at 12 months (-1.91 [-2.64 to -1.23] vs -1.72 [-2.41 to -0.73]; $p=0.25$) |
| Chakravarty et al (2016) 32 | Infants and children | Stavudine with efavirenz or ritonavir-boosted lopinavir | NA | Abacavir group with ritonavir-boosted lopinavir (six [3%]) or efavirenz (three [1%]); control group with ritonavir-boosted lopinavir (24 [4%]) or efavirenz (25 [3%]) | NA | NA | Increased risk of positive Enquête Périnatale Française score for mitochondrial toxic effects due to abacavir exposure (OR 4.76 [95% CI 2.39–9.43]) |
| Langs-Barlow et al (2013) 35 | Children | Zidovudine-lamivudine plus either efavirenz or nevirapine (most common) | NA | NA | NA | NA |
| Mega et al (2020) 36 | Children | Zidovudine, with efavirenz or ritonavir-boosted lopinavir or nevirapine | NA | Abacavir (one [1%]; median survival time 273 days [IQR 123–569]; versus control (three [3%]; median survival time 366 days [86–676]) | NA | NA | Opportunistic infections (29 [33%] of 87 with abacavir; incidence of 8.8 per 100 000 person-years vs 29 [32%] of 92 with control; incidence 6.9 per 100 000 person-years; incidence rate ratio 0.87 [95% CI 0.49–1.53]; $p=0.30$) and pneumonia (16 [18%] vs 15 [16%]) |
| Oshikoya et al (2012) 38 | Children | Zidovudine-lamivudine plus either nevirapine, efavirenz, or abacavir-ritonavir-boosted lopinavir | NA | NA | NA | NA | Skin rash events (two [2%] of 93 for abacavir vs 91 [98%] of 93 for control); gastrointestinal, including vomiting, nausea, diarrhea, and abdominal pain (16 [17%] vs 13 [14%]); pallor (one [1%] vs 11 [12%]); and headache (six [6%] vs not reported) |
| Natokonda et al (2017) 39 | Adolescents | Several; abacavir-lamivudine-efavirenz (33%) or tenofovir disoproxil fumarate-emtricitabine-efavirenz (23%) | NA | NA | NA | NA |

Age groups (infants aged 0–12 months, children aged 1–10 years, and adolescents aged 10–19 years). ART=antiretroviral therapy. HR=hazard ratio. NA=not applicable. OR=odds ratio.
p=0.63 for zidovudine vs stavudine; HR 0.88 [0.67–1.15] for abacavir vs stavudine). Two prospective studies by Patel and colleagues explored cardiovascular risks in children and adolescents, and found no effects of abacavir use on incident cardiomyopathy (adjusted odds ratio 0.7 [95% CI 0.3–1.5]). Other adverse events were lipodystrophy, mitochondrial toxic effects, change in insulin resistance, and growth outcomes (table 2).

Mortality rate was reported in seven studies. The incidence of death following abacavir treatment varied from 0.00% to 5.49% with significant between-study heterogeneity (I²=58%; p=0.026; figure 2B). Four studies compared mortality rate with ART, showing a homogeneous pooled estimate for children receiving abacavir versus those receiving stavudine or zidovudine regimens (relative risk [RR] of death 0.88 [95% CI 0.44–1.74]; τ²=16%; test for the overall effect p=0.71; figure 3). The overall mortality rate was 2.77% (95% CI 1.51–4.39; p=0.026) and viral load suppression rate was 68.02% (61.20–74.48; p<0.0001; figure 2).

Regarding efficacy outcomes, five studies reported viral load suppression at a threshold of 400 copies per mL at 6 months, and eight studies at 12 months (appendix pp 11–13). Viral suppression varied from 49.94% to 70.00% at 6 months and from 57.04% to 78.05% at 12 months, with significant heterogeneity between studies (I²=92% for the 6-month data and I²=88% for the 12-month data; p<0.0001; figure 2C).
a large prospective cohort in 2014 by Technau and colleagues, a significantly lower viral suppression rate was reported in the abacavir group than the stavudine group at 6 months (RR 0.56 [95% CI 0.43–0.72] for efavirenz and 0.49 [0.40–0.60] for ritonavir-boosted lopinavir; p<0.0001) and 12 months, regardless of the backbone therapy (RR 0.56 [0.36–0.86] for efavirenz and 0.52 [0.39–0.69] for ritonavir-boosted lopinavir; p<0.0001; appendix pp 11–14). Similar results were reported in a retrospective cohort in 2013, by the same authors. Whereas in the retrospective case–control study by Cassim and colleagues, viral suppression rates were similar between the abacavir and stavudine groups at 6 (p=0.13) and 12 months (p=0.53).

Four studies reported CD4 data related to abacavir treatment, and three of these studies compared abacavir with other ARTs. In the studies by Strehlau and colleagues and Cassim and colleagues, the CD4 percentages (defined as the proportion of all lymphocytes that are CD4 cells) were similar between the abacavir and stavudine groups over time (at 26, 32, 52, and 56 weeks; appendix p 14). In the study by Mega and colleagues, CD4 cell counts after 6 months were significantly higher in the abacavir group (9/114 vs 3/92; p=0.004).

Table 3: Relative risk ratio of mortality rate in children and adolescents who received abacavir-containing regimen compared with non-abacavir-containing regimen

Only analyses with an I² of 90% or less are displayed.

Figure 3: Relative risk ratio of mortality rate in children and adolescents who received abacavir-containing regimen compared with non-abacavir-containing regimen

Discussion

This systematic review and meta-analysis showed that overall, abacavir can be used safely and effectively for infants and children, whereas specific data on adolescents remain insufficient, which aligns with the 2021 WHO paediatric ART recommendations. The major abacavir-related toxic effect, hypersensitivity reaction, was reported in less than 2% of participants for most (seven [78%]) of nine studies. Other adverse events reported were not specifically associated with abacavir use. There was no difference in the risk of mortality for participants receiving abacavir compared with those receiving other antiretroviral drugs. Except in two South African cohort studies that highlighted a lower viral suppression rate in the abacavir group, CD4 counts and viral load at 6 or 12 months after ART initiation were not different between abacavir and stavudine-based regimens. One study showed higher CD4 count gain at 6 months for zidovudine-based regimens compared with abacavir-based regimens. Most outcomes were reported heterogeneously between studies, and except for two randomised trials, studies were considered of moderate to high risk of bias. Therefore, data interpretation needs to be made cautiously.

Hypersensitivity reaction is the main toxic effect associated with abacavir use. In this systematic review and meta-analysis, no hypersensitivity reaction cases led to worse adverse events, such as death, and symptoms rapidly resolved after abacavir discontinuation. The incidence of hypersensitivity reactions ranged from 0% to 2% in seven (78%) of nine studies which reported these reactions, and all resolved with abacavir cessation. The other two studies reported a hypersensitivity reaction incidence of 8%. The first was a prospective cohort study conducted between 2013 and 2014 in India, with a specific aim to observe the incidence of clinically diagnosed hypersensitivity reaction. This study was at high risk of bias due to a non-specific definition of the outcome, which could have led to overestimating the incidence of abacavir-induced hypersensitivity reaction. The second study was a multiregional open-label RCT conducted between 2004 and 2010, evaluating the pharmacokinetics and safety of fosamprenavir-based regimens, with abacavir used as a backbone. No data on HLA-B*5701 screening before ART initiation were available in this study, which might partly explain the high rate of an abacavir-induced hypersensitivity reaction. Screening of HLA-B*5701 is now recommended before initiating abacavir-based regimens in all people living with HIV to prevent the onset of a hypersensitivity reaction. Therefore, the low hypersensitivity reaction incidence reported in other studies might be explained by the common use of HLA-B*5701 screening before ART initiation. This screening might be more easily implemented in HIV clinics participating in research programmes, explaining why the incidence of hypersensitivity reaction reported in scientific publications is low. However, the test for HLA-B*5701 is costly and not
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We observational studies conducted in adults highlighted more serious toxic reactions. Although testing for HLA-B*5701 is a standard-of-care in high-income countries, gaps in terms of cost and access remain in low-income and middle-income countries, which could be addressed by developing rapid and inexpensive tests.41,42

Two studies conducted by Patel and colleagues25,26 did not find an increased risk of cardiovascular disease associated with abacavir use in children and adolescents living with HIV. However, in the study in adolescents, the median duration of abacavir use was less than 1 year, which might be too short in terms of drug exposure to observe cardiovascular adverse events. Several observational studies conducted in adults29,41 highlighted higher risk of cardiovascular disease for those using abacavir, whereas a pooled analysis of findings in adults enrolled in clinical trials showed no difference in the risk associated with abacavir use.43 Further studies assessing the causes of cardiovascular disease in children and adolescents receiving long-term ART are needed to better prevent comorbidities, especially in resource-limited settings in which most of this population live and where monitoring tools are scarce.44

This systematic review and meta-analysis only found a few eligible studies published between 2009 and 2022, and data collection across these studies was not homogeneous or standardised. Few studies specifically addressed abacavir safety and efficacy in adolescents, which does not allow abacavir to be recommended for this age group. Few participants initiated ART in infancy, and two of seven articles focusing on infants were conference abstracts.44,45 Most similar studies were comparing abacavir use with stavudine use, which is no longer recommended for children as a first-line regimen. None of the studies described abacavir safety and efficacy when combined with antiretrovirals introduced in the past few years, such as integrase strand transfer inhibitors, whereas dolutegravir-based regimen could lead to lower viral suppression in children with predicted abacavir resistance as found in a recent study conducted in Kenya.46 Questions remain around drug susceptibility for abacavir when used as second-line ART. Only the CHAPAS-3 trial47 identified a lower susceptibility to abacavir as a second-line regimen for virologically suppressed children receiving first-line zidovudine. This lower susceptibility could affect virological success and decrease CD4 T-cell count. No data reported on children receiving second-line ART due to unsuccessful treatment. Further research reporting results by ART rather than the regimen are needed to better address such crucial questions (eg, the efficacy of nucleoside reverse transcriptase inhibitor backbone combined with integrase strand transfer inhibitors and ART use as second-line treatment, especially in the context of unsuccessful treatment). Similarly, growth outcomes such as weight-for-age and height-for-age might be associated with the type of ART; however, few studies describe this association with conflicting results when comparing protease inhibitor-based with non-nucleoside reverse transcriptase inhibitor-based regimens.48 We found two studies comparing these outcomes according to abacavir use with no significant differences between groups.49,50 Furthermore, all health-care practitioners and research assistants (including RCTs) were unmasked to the antiretroviral regimen used, which might have affected the reporting of minor or moderate adverse events. Mortality was not reported systematically—only one study specified that no deaths occurred51—which could suggest an overestimation of our pooled mortality rate results. Additionally, the non-comparative or retrospective study design of most studies meant that most were rated to have moderate or high risk of bias, which limits our interpretation and conclusions. Finally, publication bias was reduced by the addition of grey literature in our search strategy and by discussing and sharing experiences with our paediatric HIV research network. Although our search strategy focused on articles published from January, 2009, we believe this cutoff was appropriate given that abacavir was first approved for paediatric patients in the USA in December, 2008,52 and was included in WHO paediatric ART recommendations in 2010.4 Therefore, our meta-analysis contains all studies that implemented abacavir-based regimens in line with official recommendations for dosing and clinical management.

This comprehensive systematic review summarises evidence from the past 13 years on the safety and efficacy of abacavir-based regimens in infants, children, and adolescents and aligns with the conclusions made in previous systematic reviews.53,54 Systematic reviews conducted in adults highlighted more serious toxic effects, such as cardiovascular diseases;55 however, our findings support the recommendation to use abacavir as the preferred first-line regimen for infants and children. Specific data on adolescents are insufficient to provide recommendations for this age group. Future individual-level meta-analyses should further assess the efficacy of abacavir as nucleoside reverse transcriptase inhibitor backbone, especially when combined with newly introduced integrase strand transfer inhibitors. To conclude, we advocate for further research in infants, children, and adolescents living with HIV to monitor and assess ART toxicity and safety, improve ART tolerance and adherence, and improve the quality of life for this population.

Contributors
JJ and VL conducted the search strategy and data extraction with support and discussions with LS-L and MHDRT. JJ, LS-L, MHDRT, and VL did the data analyses. JJ wrote the first draft of the manuscript with further input from all coauthors. All authors contributed to the protocol development, reviewed, and edited the manuscript. JJ had final responsibility for the decision to submit for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication. JJ and VL have accessed and verified all the data in the study.
Declarations of interest
CLT received consultancy fees from WHO and the International AIDS Society. JO received consultancy fees from WHO to develop this meta-analysis. VL received a consultancy contract for the University of Toulouse from WHO to develop and conduct this Review. All other authors declare no competing interests.

Data sharing
All data are included in the manuscript and appendix.

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